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# SYSTEMIC RETICULOENDOTHELIAL GRANULOMA

## NONLIPOID RETICULOENDOTHELIOSIS AND SCHÜLLER-CHRISTIAN DISEASE

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During the last few decades morbid conditions in the reticuloendothelial system have more and more aroused the interest not only of pathologists but of clinicians. Several anatomically, and to some extent clinically, characteristic but, as far as can be judged, pathologically different systemic diseases have been described. For want of concise, characteristically etiologic, clinical or anatomic designations, these conditions have been labeled with the names of the research workers who first investigated the different types of disease—Gaucher's disease, Niemann-Pick disease and Schüller-Christian disease. The latest addition to these diseases is that named Letterer-Siwe disease by Abt and Denenholz.[1]

When judging the character of a morbid condition in the reticuloendothelial system one should not shut one's eyes to the great difficulties encountered. One is apt to yield to the temptation to limit the conception of the disease too strictly, to regard variations as different diseases or, on the contrary, to include conditions that subsequent wider experience teaches do not belong there. A classification of a case of disease will not infrequently be rather subjective. Therefore, it is not to be wondered at that opinions still differ, that cases are referred by one author to a type of disease to which others perhaps do not consider they belong and that, on the other hand, a secondary change or a casual complication is described as a special disease.

Like Abt and Denenholz [1] and van Creveld,[2] Siwe [3] has divided into two groups cases of disease of the reticuloendothelial system not

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1. Abt, A. F., and Denenholz, E. J.: Letterer-Siwe's Disease: Splenohepatomegaly Associated with Widespread Hyperplasia of the Nonlipoid-Storing Macrophages; Discussion of So-Called Reticulo-Endothelioses, Am. J. Dis. Child. **51**:499 (March) 1936.

2. van Creveld, S.: Rev. franç. de pédiat. **13**:314, 1937.

3. Siwe, S.: Ztschr. f. Kinderh. **55**:212, 1933.

belonging to the Gaucher, Niemann-Pick or Schüller-Christian types: (1) cases in which an acute infection was present which was regarded as the cause of the disease and (2) cases in which no positive evidence could be found of the presence of an etiologically significant infection.

Among the latter group (Letterer-Siwe disease) are classed the cases reported by: Letterer [4] (1924), Akiba [5] (1926), Guizetti [6] (1931), Podvinec and Terplan [7] (1931), Gittins [8] (case 4, 1933), Siwe (1933), Foot and Olcott [9] (1934), Roussy and Oberling [10] (1934) and Abt and Denenholz (1936). Since the publication of Abt and Denenholz's work no additional case has been recorded which satisfies the criteria set up.

The cases reported by the following investigators have been classified as reticuloendothelioses due to infection: Schultz, Wermbter and Puhl [11] (1924), Krahn [12] (1926), Sherman (1929), Uher [13] (1933), Gittins (case 2, 1933) and van Creveld and ter Poorten [14] (1935).

The two diseases mentioned here, infectious reticuloendotheliosis and Letterer-Siwe disease, have been combined under the name of nonlipoid reticuloendotheliosis, in contradistinction to Schüller-Christian disease, which is classified among the general xanthomatoses on account of the lipoid content of the infiltrations of reticulum cells. These cholesterol deposits in the granulomas have been rather generally regarded by pathologists and clinicians as pathognomonic of Schüller-Christian disease. This view has, however, been opposed by certain authors (Ceelen,[15] Wätjen [16] and Thannhauser and Magendantz [17]), who maintain that the cholesterol deposit in the proliferations of reticulum cells is a secondary and facultative phenomenon. As the reasons for such a point of view seem to be at least as sound as the evidence put forward in support of a contrary opinion, the question of

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4. Letterer, E.: Frankfurt. Ztschr. f. Path. **30**:377, 1924; Klin. Wchnschr. **13**:1046, 1934.
5. Akiba, R.: Virchows Arch. f. path. Anat. **260**:262, 1926.
6. Guizetti, H. U.: Virchows Arch. f. path. Anat. **282**:194, 1931.
7. Podvinec, E., and Terplan, K.: Arch. f. Kinderh. **93**:40, 1931.
8. Gittins, R.: Arch. Dis. Childhood **8**:367, 1933.
9. Foot, N. C., and Olcott, C. T.: Am. J. Path. **10**:81, 1934.
10. Roussy, G., and Oberling, C.: Wien. med. Wchnschr. **84**:407, 1934.
11. Schultz, A.; Wermbter, F., and Puhl, H.: Virchows Arch. f. path. Anat. **252**:519, 1924.
12. Krahn, H.: Deutsches Arch. f. klin. Med. **152**:179, 1926.
13. Uher, V.: Virchows Arch. f. path. Anat. **289**:504, 1933.
14. van Creveld, S., and ter Poorten, F. H.: Arch. Dis. Childhood **10**:125, 1935.
15. Ceelen, W.: Deutsche med. Wchnschr. **59**:680, 1933.
16. Wätjen, J.: Beitr. z. path. Anat. u. z. allg. Path. **96**:443, 1935.
17. Thannhauser, S. J., and Magendantz, H.: Ann. Int. Med. **11**:1662, 1938.

the importance of the storage of cholesterol in the differential diagnosis between Schüller-Christian disease and certain other systemic reticuloendothelioses must be regarded as unsettled.

On the basis of 2 cases of systemic reticuloendotheliosis which I investigated, several disputed problems concerning these diseases will be elucidated and discussed.

## REPORT OF CASES

CASE 1.—*History.*—The patient, a girl aged 4 months, was born on June 22, 1937 at full term and had a birth weight of 3,500 Gm. She was breast fed for three and a half months and afterward given supplementary feeding. She was the only child of healthy parents who had negative Wassermann reactions. The child was in good health until she was 1 month old. She then had a dermatosis on the cheeks, which soon spread over the entire trunk. With the appearance of a

Fig. 1 (case 1).—Eruption resembling but differing from seborrheic eczema on back, nape of neck and chest.

slight catarrhal infection the cutaneous disease became worse, and the mother consulted a physician on October 16. At this examination the child was found to be somewhat underweight, for which supplementary feeding with milk and cream, half and half, was prescribed, and to have anemia, for which she was given iron preparations. Ointments were applied to the cutaneous lesions, which were regarded as eczema. When the child was again seen two or three weeks later, the eczema had improved, but the anemia had progressed in spite of the iron medication. For that reason she was sent to the Children's Hospital on November 5, at which time she was more than 4 months old. It may be mentioned that she had cut her first tooth at the age of 3½ months and had afterward cut two more front teeth in quick succession.

*Examination and Course.*—On admission the child was in poor condition, unable even to raise her head from the pillow. She was somewhat thin (weight 5,100 Gm.) and markedly pale. The temperature was 37.8 C. (100 F.). On the chest, back and nape she had an eruption, which at a cursory glance appeared to be seborrheic eczema but on closer examination was found to be entirely different (fig. 1.) The lesions consisted of sharply defined linear ridges and

islands of slightly desquamated skin, separated by long and narrow furrows or more superficial, irregularly outlined areas of skin where the corium was exposed. Here and there were petechiae. In the inguinal folds there was also a typical intertrigo. The pharynx was pale. There were hemorrhages in the gingiva close to the teeth. The reactions to the tuberculin (0.1 mg.) and Wassermann tests were negative. The urine was not increased and was free from albumin and sugar.

The most striking feature of the examination was noted in the calvarium. Here there were several palpable, asymmetrically situated lesions, varying in size from that of a pea to that of a 5 cent piece, with firm, sharply defined edges, in which

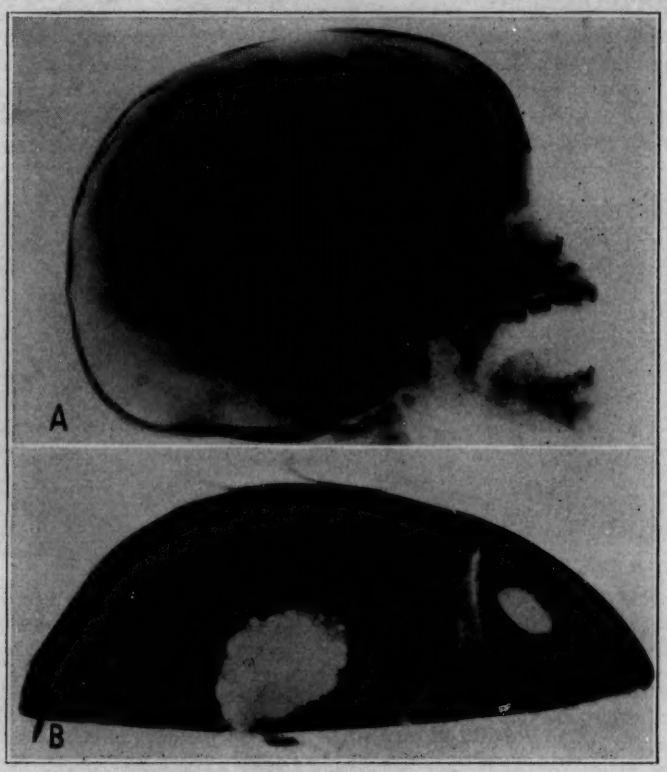


Fig. 2 (case 1).—Roentgenograms showing osseous lesions of the cranium. *A* was taken before death and *B* after death.

bone seemed to have been replaced by a membrane of connective tissue. Better than any description is the appearance of these osseous lesions in the roentgenograms, especially in the one taken after death (fig. 2 *B*).

The hemoglobin content was 40 per cent; the erythrocytes numbered 2,140,000. The anemia was uncharacteristic; there were signs of good regeneration, with 3.5 per cent reticulocytes and 4 normoblasts per 200 leukocytes. The size of the red blood corpuscles was from 7.4 to 7.7 microns. The number of leukocytes was 9,200 (38 per cent lymphocytes, 3 per cent monocytes, 55 per cent segmented neutrophils, 2 per cent nonsegmented neutrophils and 2 per cent transitional forms) and of platelets 143,000. The coagulation time was normal, and the bleeding time

was two minutes. The sedimentation rate was 7 mm. (maximum pathologic value, 43). The cholesterol in the blood serum was 75 mg. per hundred cubic centimeters. There were no signs of increased hemolysis. Van den Bergh's test was negative; no urobilin or urobilinogen was demonstrable in the urine.

The spleen extended 2 fingerbreadths below the thorax and was firm. The liver also extended for a distance of 2 fingerbreadths below the thorax. There were no noteworthy swellings of the lymphatic glands.

During the subsequent course of the disease the blood values gradually fell, and the last counts made showed the hemoglobin content to be 32 per cent and the erythrocyte count 1,460,000. The power of regeneration was still good: 12.6 per cent reticulocytes and 32 normoblasts per 200 leukocytes. The number of leukocytes was 12,000, with lymphocytosis. Retraction time was delayed and the bleeding time prolonged; masses of petechiae appeared in the mouth and on the skin; bleeding occurred freely in the cutaneous lesions. The sedimentation rate was 7 mm. The spleen was somewhat enlarged. The temperature was slightly elevated (fig. 3) with peaks for some days up to 38 or 39 C. (100.4 or 102.2 F.). There were no palpable glandular swellings. The girl died on the ninth day after admission, at the age of 4½ months, after an illness lasting about three months.

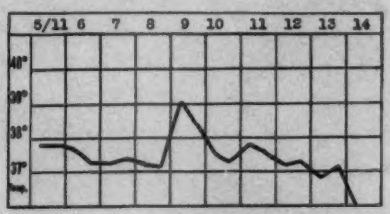


Fig. 3 (case 1).—Fluctuation in temperature over a ten day period in the hospital.

The clinical diagnosis was: anemia with *Lückenschädel*[18] (suspected reticuloendotheliosis).

*Necropsy.*—Macroscopic Examination: The body was rather thin. A flamy and scurfy eczema was spread over large areas of the trunk.

In the cranium there were lesions as large as the tip of a man's finger, partly in the posterior part of the lateral portion of the coronal bone and at the tubera parietalia on the left side and partly behind the posterior margin of the coronal bone, somewhat involving this bone, on the right side. The base of the lesions was covered with a solid membrane of connective tissue. The bone decreased in thickness toward the lesion within a border 4 to 5 cm. in width and was scurfy and somewhat yellowish; the osseous lesion thus gave the impression of proceeding from without inward.

There were no evident changes at the base of the skull. The pituitary body showed no abnormality macroscopically. The brain was pale but without any evident changes.

The lungs were aeriferous and tough and did not have any enlarged hilar glands.

The small intestine was normal. In the large intestine there were small, punctiform, blackish gray hemorrhagic residues. The mesenteric glands were rather large and brownish red to vermilion. The spleen weighed 65 Gm., was

18. Skull with gaps or lacunas in the bone.

rather firm and had a smooth brownish red surface; the cut surface was also smooth and reddish brown, with an ill defined mottling tinged with grayish white.

The liver weighed 210 Gm. The surface was smooth and grayish yellow. The cut surface was smooth, dry and somewhat streaked light and dark grayish yellow; it was otherwise unmarked and was distinctly tough.

The kidneys and the adrenal bodies were pale; otherwise they were normal.

The ovaries were small and white.

The marrow in the tubular bones, as well as in the sternum, was rather abundant and varied from vermilion to deep red.

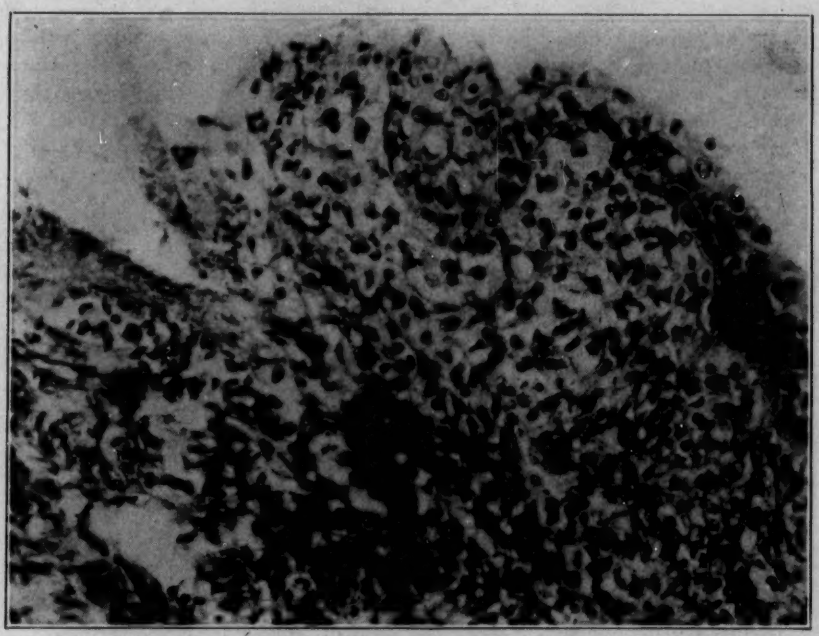

Fig. 4 (case 1).—Necrotic portion of the epidermis, with underlying extensive reticuloendothelial proliferation.

Microscopic Examination (Dr. Gellerstedt): Skin. In stretches of the stratum papillare cutis there was a peculiar cellular proliferation, mixed with a few round cells, consisting of cells of irregular forms with round, oval or polymorphous nuclei. The cells were protoplasmic and were partly joined by protoplasmic projections into an evident reticulum. The meshes of this reticulum were large in places and had given rise to vesicular structures which, at their greatest size, appeared to detach the epidermis from the underlying layer. This was evidently reticuloendothelial proliferation (fig. 4). Owing to the cellular neoplasm beneath, the epidermis had in some places undergone degenerative changes, which had led to atrophy, necrosis and desquamation, but it is noteworthy that the cutaneous lesions thus occurring showed a slight leukocytic reaction and had necrotic, fibrin-saturated bases. Some of the smaller vessels of the cutis showed marked endothelial proliferation, evidently with obliteration or constriction of the lumen.

Cranium. The cancellous lesions in the bone were filled with granulomatous tissue, which for the most part consisted of the same reticuloendothelial elements as in the skin but in several places formed compact, protoplasmic accumulations of cells reminiscent of epithelioid cellular tissue. To some extent there was development of fibrillar intercellular substance and a fibrous structure in the reticulum, which caused certain areas of the granuloma to appear more fibrous than others. In some places there was a suggestion of necrosis in the cellular tissue. Moreover, there occurred islands of bone marrow, rich cells, of somewhat normal composition. The margins of the bones limiting the granulomatous foci were sharply defined, and there was no evidence of osseous neoplasms, but lacunar resorption of bone (fig. 5) was observed. Osteoblast-like elements were

Fig. 5 (case 1).—Section from a lacuna in the skull showing the sharply defined margins.

also found scattered in the granulomatous tissue. This tissue contained no lipoid substances, but eosinophilic leukocytes were found here and there. The inner surface of the dura had decomposed into a thin, loose layer of cells having an evident reticular structure.

Lymphatic glands. There was enormous, diffuse reticuloendothelial proliferation, with great reduction of the lymphoid tissue, of which only a few rudimentary lymph follicles remained. The reticulum cells often formed compact, protoplasmic accumulations, probably representing filled sinuses, but the picture differed greatly from that of the so-called sinusal catarrh by its diffuse character. Here and there necrotic processes were seen in the epithelioid cell-like foci. There was no myeloid reaction, and no lipoids were observed. An occasional eosinophilic leukocyte was seen.

Thymus. There was intensive reconstruction of the parenchyma due to the enormous proliferation of the reticuloendothelium; the marrow and cortex were no longer distinguishable. As in the lymphatic glands, agglomerations of epithelioid-like cells had also been formed. There were curious obliterating cellular proliferations of (lymphatic?) vessels, the endothelium of which had assumed a palisade position. Large, calcified and degenerating Hassall bodies and isolated eosinophilic cells were found. There were no lipoids except in one or two small necrotic areas.

Bone marrow. The marrow of the ribs and tubular bones was rich in cells, with marked erythropoiesis but was otherwise approximately normal. The bone marrow reticulum was hyperplastic and pronounced, but it did not form any diffuse or focal proliferation. The vascular endothelium was also swollen in places. No lipoids were present.

Spleen. The pulp contained abundant blood and cells. A moderate reticulosis was seen diffusely in the pulp and more clearly in the perifollicular zone. Scattered eosinophilic leukocytes were found. There was abundant ferruginous pigment in the vascular and reticulum cells but only in circumscribed areas. At one place there was an area rich in blood, resembling an infarct in which the reticular cells had phagocytosed lipoid granules. There were small groups of myeloid elements.

Liver. The reticuloendothelial system was not markedly proliferative. The parenchyma was normal.

Adrenal bodies. The cortex was poor in lipoid. The marrow was to some extent replaced by fibrous tissue.

Ovaries, intestines and kidneys. No abnormalities were found.

*Comment.*—According to Siwe, the disease defined by him is characterized by: (1) enlargement of the spleen and liver; (2) hemorrhagic diathesis, chiefly manifested by petechial exanthema or purpura; (3) general enlargement of the lymphatic glands, as a rule not pronounced in vivo and seemingly of noninfectious origin; (4) secondary anemia of a progressive type, generally with a normal leukocyte count; (5) occurrence, neither hereditary nor familial, exclusively in infants and young children, unknown etiology, fatal prognosis and variable duration (from a few weeks to several years); (6) localized skeletal changes in the form of tumorous formation or osseous lesions in some cases, and (7) general hyperplasia of the cells of the reticuloendothelial system, which may focally assume a tumor-like proliferation, especially in the spleen, liver, lymphatic glands, thymus, skin and bone marrow, and usually signs of a hemorrhagic tendency but no constant storage of fat, lipoid or Gaucher's substance in the cells.

In the case reported here the clinical symptoms seem to agree in all respects with those Siwe considered characteristic of the disease defined by him. It is a nonlipoid reticuloendotheliosis of unknown causation in an infant, with localized skeletal changes, progressive secondary anemia, petechial exanthema and enlargement of the liver and spleen. The only respect in which there may be some doubt is the possibility of there being an etiologic connection between the reticuloendothelial

proliferation and the acute infection the girl is said to have had at the beginning of her illness. If this connection exists the case should be referred to the so-called infectious reticuloendothelioses. But these catarrhal symptoms were not the first signs of disease; the cutaneous lesions that persisted during the entire course and which the histologic examination revealed to be due to a reticuloendothelial proliferation antedated them by about a month. Such a cutaneous disease as seborrheic dermatitis or eczema occurs remarkably often as an early symptom in systemic reticuloendothelial diseases. This was true in the second case of this report and in a number of cases of Schüller-Christian disease (Hand,[19] Henschen,[20] Lichty,[21] Merritt and Paige,[22] Wätjen and others). In these cases a proliferation of reticulum cells was usually shown in the skin. This points to a causal connection between the cutaneous changes and the reticuloendothelial proliferation.

That the cutaneous changes at the end of the disease can be fully explained by the demonstrated cutaneous reticuloendothelial proliferation is beyond doubt. On the other hand, it may be disputed whether the dermatosis in its origin was, from a dermatologic point of view, a common form of seborrheic dermatitis or eczema. At an early stage the cutaneous disease did not, however, differ clinically from the maladies mentioned. As neither of these types of dermatosis is pathogenetically specific but may occur as an expression of varied irritations and general or local disturbances, it is probable that in these cases of reticuloendotheliosis the dermatosis is brought about by the proliferation in the skin. On the other hand, it is known that the reticuloendothelial granulomas are not infrequently localized where trauma or irritation has previously existed. The infiltration of the skin might, therefore, be a phenomenon secondary to a commonplace dermatosis. The dermatosis can hardly have been of any etiologic importance in the disease in any other respect.

At all events, a dermatosis was present in this case even before the appearance of the slight catarrhal symptoms. The infection was not severe and was not at all noticeable during the child's stay at the hospital. It therefore seems improbable that such a slight, relatively transient, catarrhal infection of the upper air passages produced this progressive reticuloendothelial proliferation. The infection in this case

19. Hand, A.: Arch. Pediat. **10**:673, 1893; Am. J. M. Sc. **162**:509, 1921.

20. Henschen, F.: Acta pædiat. (supp. 6) **12**:1, 1931.

21. Lichty, D. E.: Lipoids and Lipoid Diseases: Xanthomatosis (Schüller-Christian's Type), Arch. Int. Med. **53**:379 (March) 1934.

22. Merritt, K. K., and Paige, B. H.: Xanthomatosis (Schüller-Christian Syndrome): Report of Case with Necropsy, Am. J. Dis. Child. **46**:1368 (Dec.) 1933.

was not more marked than that occurring in several of those cases of reticuloendotheliosis classified as cases of Letterer-Siwe disease.

The clinical feature that suggested reticuloendotheliosis was the prominent lesions in the calvarium. On account of the localization of the osseous destructions, the malady was at first thought to be Schüller-Christian disease. No positive clinical evidence was obtained, however, as to the type of reticuloendotheliosis. The absence of hypercholesterolemia was of no importance in this respect. The child's age and the subsequent course of the disease, with its symptoms of progressive anemia and hemorrhagic diathesis, were nevertheless considered to argue more in favor of a nonlipoid reticuloendotheliosis than Schüller-Christian disease. The differential diagnosis between these two types of disease is, of course, a pathoanatomic problem and was in this case made in favor of the former disease. There were no agglomerations of cholesterol-containing foam cells in the granulomas. The cells containing lipoids did not occur in greater numbers than in those cases previously classified as nonlipoid reticuloendotheliosis.

CASE 2.—The patient, a boy, was born March 4, 1936. He weighed 3,600 Gm. at birth and was breast fed. He was the only child of healthy parents, developed normally and showed no symptoms of disease, including cutaneous lesions, during the first year of life. At the end of his second year he had eczema of the scalp, beginning with ordinary seborrhea and followed by the formation of crusts on fluid-exudating surfaces. One or two months later there were intensely itching efflorescences scattered over the back. For some time before his admission there was also an eczematous eruption on the arms and legs, accompanied by severe itching. At the same time as the appearance of the eruption on the scalp, the mother noticed a discoloration of the palate at a spot on the inside of the margin of the teeth. This discolored area gradually began to swell into the form of a thickened ridge. After some time similar changes also appeared on the left side. The boy was treated for the lesions of the skin and oral mucous membranes at a provincial hospital from April 27 to June 23, 1938. He was admitted to the Children's Hospital on July 11, when he was 2 years and 4 months old.

*Examination and Course.*—First Admission: The child was somewhat pale but in rather good condition. He weighed 13,900 Gm. and was free from fever. The sedimentation rate was 8 mm. There were no abnormal signs in the internal organs. The spleen was not enlarged, the liver extended to the margin of the thorax in the mamillary line and there were no palpable swellings of the lymphatic glands. The skin was, on the whole, dry. The scalp was covered with crusts, from which there was slight exudation. On the back, in several places on the arms and legs and on the trunk, there were readily scaling, partly papulous efflorescences with evident marks of scratching. In the oral cavity on the right side of the hard palate, close to the margin of the teeth, there was a smeary, coated ulceration with elevated margins, about 2 cm. long. The base of this ulcer was smooth, without any visible granulation. On the left side, close to the margin of the teeth, there was a yellowish white discolored area, about the size of a cent, with a reddened margin. There were some enlarged lymphatic glands, about the size of peas, in the neck. The hemoglobin content was 78 per cent, and there were 8,900 leuko-

cytes (42 per cent lymphocytes; 8 per cent monocytes; 48 per cent segmented neutrophils, and 2 per cent nonsegmented neutrophils). The reactions to the Wassermann and Mantoux (1 mg.) tests were negative.

The dermatosis was treated as eczema. The boy was discharged after three days with the diagnosis of eczema and chronic ulcerative stomatitis and was told to return after some weeks.

After he left the hospital the itching continued and the dermatosis spread over the entire trunk and the extremities. The eruption was treated as eczema with ointments and coal tar by a dermatologist. The boy's condition varied. The itching was troublesome and disturbed his sleep. On November 2 he had icterus, probably from acute hepatitis. The feces were light gray and the urine dark brown. During the attack of icterus the itching increased, even in parts of the body without eczematous lesions. In the middle of November the icterus began to subside. The elevated ridge on both sides of the palate had by then increased. During the previous week there had been much bleeding from those places on the skin which the patient had been able to scratch, especially the scalp. He was transferred from the provincial hospital to the Children's Hospital on November 22.

Second Admission: His general condition was worse. He was thin and pale, with sunken cheeks. The scleras and back were somewhat yellowed. The temperature was 38.5 C. (101.3 F.) and the weight 11.4 Kg. There were extensive cutaneous lesions, particularly on the trunk and the scalp, which was covered with a caked mass of residue of ointments, dried blood and secretion. On the back there was a thick cake of dried ointment and secretion, twice the size of a man's palm. On the trunk there were numerous marks of scratching and some scattered, small, papulous efflorescences. On the lower part of the legs there were suggillations and slightly discharging efflorescences. In the right axilla there was a large eczematous spot, with necrosis in the center.

The pharynx showed no abnormality, and the tonsils were not hypertrophic. In the oral cavity on both sides of the hard palate, close to the teeth, there was a greasy coated ridge with yellowish white spots, but otherwise the surfaces were fairly smooth.

In the neck, axillae and groins there were numerous firm glands, ranging in size from that of a grain to that of a small pea as well as somewhat larger, almost bean-sized glands.

A systematic roentgen examination of the skeleton failed to reveal abnormalities anywhere except in the right femur. In the upper quarter of this bone, immediately below the area of the trochanter minor, there appeared some partly confluent, osseous lesions (fig. 6), rather well defined and occupying an area of about 4 by 1.5 cm.

The heart was normal. There was a faint dulness and slight weakening of the breath sound at the rear of the right lung but no adventitious sound. The liver was palpable, with a sharply demarcated edge on a level with the umbilical plane, and was firm. The spleen was not palpable.

Examination of the blood showed a hemoglobin content of 60 per cent, 3,950,000 erythrocytes, 16,200 leukocytes (3 per cent eosinophils, 37 per cent segmented neutrophils, 18 per cent nonsegmented neutrophils, 31 per cent lymphocytes and 11 per cent monocytes) and 334,000 platelets. The bleeding time was more than half an hour, and the coagulation time was twenty-one minutes. Retraction was 4 mm. after half an hour. The sedimentation rate was 30 mm. The urine was free from albumin and sugar and had no sediment, but bile pigments were demon-

strable. Tests for urobilin and urobilinogen were negative. The blood pressure was 90. The feces were dark, and bile pigments were demonstrable in them.

Biopsy of an inguinal gland on November 25 (Dr. Gellerstedt) showed: "Chiefly signs of sinusal catarrh, that is, signs of a rather chronic infectious irritation, a kind of lymphadenitis. In one or two places there were small agglomerations of epithelioid cells of a primary tuberculid type. Several of the cells of the lymphatic glands, in both sinuses and pulp, showed fatty degeneration. Moreover, there were small agglomerations of hemosiderin. The histologic picture did not

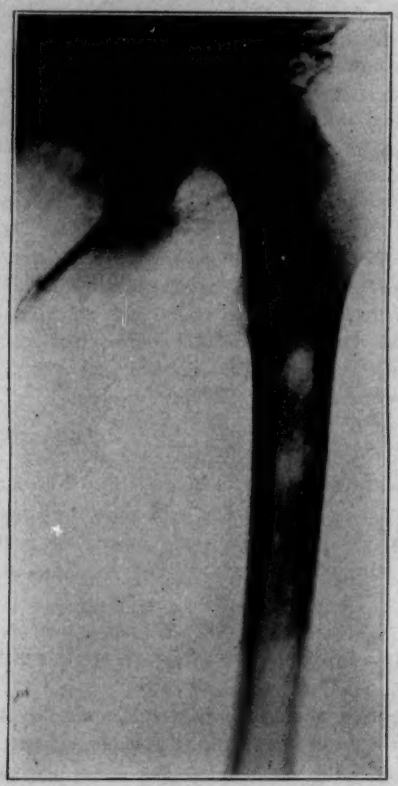

Fig. 6 (case 2).—Circumscribed osseous destruction of the right femur.

resemble that of reticuloendotheliosis. It was more like Schaumann's disease or Boeck's sarcoid. The diagnosis of these diseases is by no means certain from this examination of the inguinal lymphatic gland."

On November 26 the hemoglobin content was 40 per cent, and there were 2,300,000 erythrocytes and 17,000 leukocytes (59 per cent segmented neutrophils, 9 per cent nonsegmented neutrophils, 1 per cent neutrophilic myelocytes, 25 per cent lymphocytes and 6 per cent monocytes). There were 5.8 per cent reticulocytes, and there was 1 normoblast per 27,000 red blood corpuscles. The temperature varied (fig. 7) from 37.5 to 38.6 C. (99.5 to 101.5 F.). Transfusion of 100 cc. of blood from the mother was performed on November 27. Two days later the hemoglobin content was 49 per cent.

When the bleeding tendency had decreased and the crusts had been softened and removed, it was possible to investigate the cutaneous lesions more closely (fig. 8). It was then found that the eruption on the back consisted of numerous small, yellowish red or red hemorrhagic papules, varying from the size of a

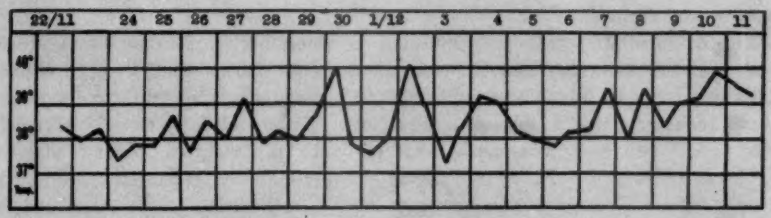


Fig. 7 (case 2).—Fluctuation in temperature over a three week period in the hospital.

Fig. 8 (case 2).—Papular eruption on the back.

pinhead to that of a peppercorn, intermingled with small, yellowish red, sunken areas, so that the involved area resembled a shagreened surface. Similar lesions were found on the scalp. On other parts of the body there were marks of scratching and solitary, small hemorrhagic papules. The patient was troubled by severe itching now and then. The extirpation of the lymphatic gland caused extensive

bruises on the upper part of the leg, scrotum and penis. On both sides of the hard palate, close to the teeth, there was a greasy coated, canaliculate ulceration, medially bounded by a relatively smooth ridge, 3 or 4 cm. long, 1 cm. wide and 0.5 cm. high, with scattered yellowish papules but otherwise smooth. The adjacent teeth had loosened in their alveoli. There was a yellowish gray, greasy coating on the teeth and the ulceration.

The sedimentation rate was 33 mm. on December 6. Examination of the blood showed a hemoglobin content of 50 per cent, 3,050,000 erythrocytes, 22,200 leukocytes (7.3 to 7.8 microns) (0.5 per cent eosinophils, 56 per cent segmented neutrophils, 8.5 per cent nonsegmented neutrophils, 28 per cent lymphocytes and 7 per cent monocytes), 8.7 per cent reticulocytes, 567,000 platelets and 1 normoblast per 28,000 red blood corpuscles. The coagulation time was fourteen minutes; the retraction was normal. The test for bile pigment was positive and for urobilin negative. The temperature varied from 38 to 39 C. (100.4 to 102.2 F.), and the general condition was worse. The bleeding tendency had decreased somewhat. New efflorescences had appeared on the abdomen, beginning as pinhead-sized, yellowish red or red papules, with sometimes glossy and sometimes slightly desquamating surfaces. There were subungual hematomas. An infiltrate had arisen in the scar resulting from the blood transfusion. There was a similar infiltrate in the scar after the extirpation of the gland. On December 12 the sedimentation rate was 37 mm., and examination of the blood showed a hemoglobin content of 46 per cent, 2,400,000 erythrocytes, 8,200 leukocytes (4 per cent eosinophils, 53 per cent segmented neutrophils, 5 per cent nonsegmented neutrophils, 34 per cent lymphocytes and 4 per cent monocytes), 0.3 per cent reticulocytes, 143,000 platelets and no nucleated red cells. The coagulation time was sixteen minutes; the retraction was normal. The tests for bile pigment and urobilin were positive.

The patient was increasingly troubled by itching. During the last few days before death there was bleeding from the ulcers, the oral cavity and from the efflorescences on the back.

*Necropsy.*—Macroscopic Examination: The body was that of a rather emaciated boy, with distended abdomen and slightly icteric skin. The skin of the front of the trunk, of the scalp and particularly of the back was covered with small, hemorrhagic papules. There was evidence of subungual bleeding.

The heart was flaccid, and the valves were normal. The lungs were pale and noninfiltrated; there were numerous lymph nodes, up to the size of a hazelnut, in the hili and the mediastinum, some of which were hemorrhagic.

The liver was enlarged and firm and weighed 740 Gm. It was yellowish green, with here and there paler, yellow areas. In the portal region there were abundant lymph nodes, up to twice the size of a hazelnut. The spleen weighed 80 Gm. and was firm.

Numerous lymph nodes, generally hemorrhagic, were in the mesentery, varying in size from that of a bean to that of a hazelnut. There were also lymph nodes, ranging from the size of a pea to that of a bean, in the neck, axillas and groins.

The lobate, pale kidneys weighed 98 Gm. The adrenal bodies showed no macroscopic changes.

In the oral cavity on either side, parallel to the teeth, was a protuberant infiltration, 5 cm. long, with an ulcerating grayish center.

In the upper part of the diaphysis of the right femur there were two areas, about the size of walnuts, in which the dark red bone marrow turgidly filled the enlarged marrow cavity.

Microscopic Examination (Dr. Gellerstedt): There was a diffuse reticuloendothelial proliferation with a varying, subacute, inflammatory element. The process was localized to a relatively uniformly thick layer, confined to the stratum papillare cutis. The covering epidermis was in general attentuated and seldom infiltrated, but in several places it was necrotic or had been shed, and disseminated, superficial, erosive ulceration had arisen over the developing masses of cells. These agglomerations were composed of pale-celled, round or oval, plasmatic elements with irregular, cystiform, frequently horseshoe-shaped or calceolate, nuclei. A few cells were found to contain a moderate quantity of lipoid substances, partially double refractive (fig. 9). There was also a more or less abundant

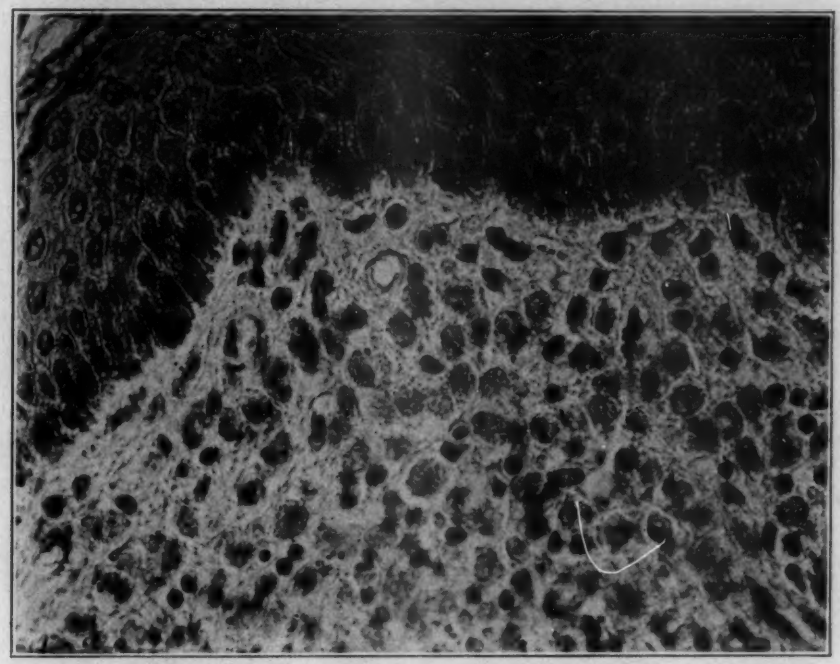

Fig. 9 (case 2).—Subepidermal reticuloendothelial proliferation; some cells contain lipoid granules (black color).

quantity of fat granules in the fibroblasts of the cutaneous connective tissue. Some proliferation of adventitial cells was seen in the small vessels in the deeper parts of the cutis.

Oral mucous membrane. Below and surrounding the ulcer there extended an intensive, tumor-like cellular infiltration, for the most part composed of proliferating reticulum cells of the type found in lymphoid tissue. These cells were either round, oval, polygonal or elongated, with cystiform, dented or otherwise polymorphous nuclei, or they were of a pronounced epithelioid type. In several places they appeared to be large, polymorphonuclear, balloon-shaped, swollen foam cells; at other places they seemed to resemble densely packed pseudoxanthoma cells with small, dark nuclei (fig. 10). The two last-mentioned types of cells, in particular, contained a rich deposit of lipoids, mainly doubly refractive. Deep down, the

submucous cellular masses around and between the lobuli of the mucous membrane were interspersed with close strands of connective tissue, within which spindle cell, plasmatic elements predominated. In the neighborhood of the ulcer there was, of course, an evident inflammatory admixture, with a strikingly large number of eosinophilic leukocytes.

Lymphatic glands. The glands from various regions showed essentially the same changes. The normal structure was to a great extent impaired by a reticulo-endothelial proliferation, which exceeded the boundaries of the lymph sinuses and in several places surrounded or penetrated into the secondary follicles, frequently in an eccentric arrangement. The fibrillar lymph reticulum was destroyed

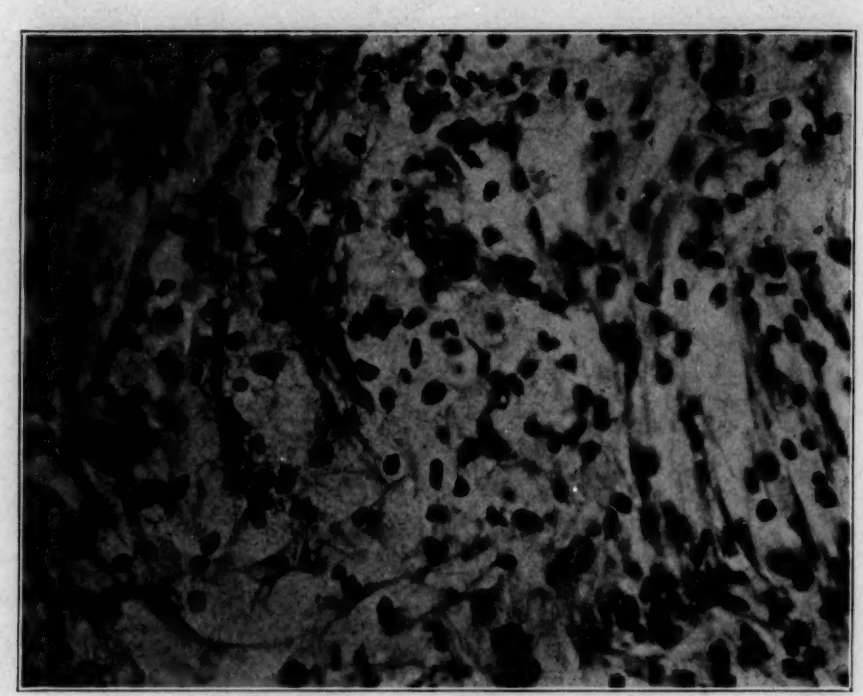

Fig. 10 (case 2).—Section from the ulcer in the mouth. There is foam cell infiltrate in the lower parts of the submucosa.

in several places. Foam cells were found only sparsely and were not so well developed as in the oral mucous membrane. In one or two lymphatic glands numbers of intracellular yellow pigment granules were seen which did not show any reaction to iron but which assumed a weak lipoid pigment. Otherwise the lipoid content of the infiltrated masses in the various lymphatic glands was variable, generally rather scanty and unequally distributed.

Spleen. There was diffuse and focal, intense cellular reticulosis. The individual reticulum cells in this organ were in general larger, rounder and richer in photoplasm, with round, cystiform nuclei. There were no evident foam cells. The lipoid content was variable and not particularly high. Frequently the cellular infiltration was seen to be more intense around and in the malpighian bodies,

which on that account appeared to be abortive or totally destroyed. Besides, there were signs of a subacute splenitis.

Bone marrow. The foci in the bone marrow of the femur, visible in the roentgenogram, consisted of lipoid cell granulomas (fig. 11) or lipoid cell reticulomas with a regular foam structure of the large, round, pale, often polymorphonuclear cells. The fatty substances were also here for the most part doubly refractive. The foci were, as a rule, sharply defined, and in the adjacent areas spots of incipient calcification could be seen in the apparent reticulum; also diffuse calcium deposits in the adventitia of some arterioles. No injury to the bone was demonstrable in the area of the foci. Otherwise the bone marrow, as in the sternum, was pronouncedly red and of apparently normal composition.

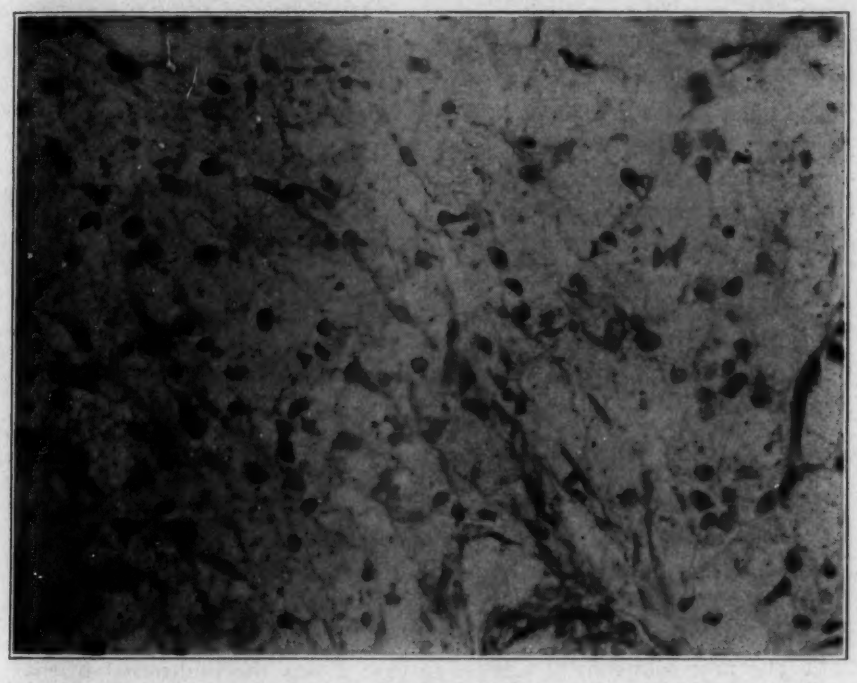

Fig. 11 (case 2).—Section from the decalcified part of the right femur showing abundant lipoid cell granuloma (foam cells).

Liver. One could see there had been reconstruction and partial elimination of the acinous structure by means of broad rows of connective tissue, which were mostly confined to the periportal tissues. In the connective tissue were numerous new formations of small bile ducts and young vessels, with inflammatory infiltrations of scattered plasma cells and pus bodies and small masses of lymphocytes. Nowhere was there any evident reticuloendothelial proliferation. The Kupffer stellate cells were normal. There was no foam cell infiltration. The parenchyma of the liver was the seat of a bile-capillary stasis and a moderate droplet fatty degeneration, diffusely disseminated. Thus, pathoanatomically, the liver showed interstitial chronic or subchronic fibrotic hepatitis.

Thymus. There was pronounced involutive atrophy.

Kidneys, adrenal bodies and pancreas. No abnormalities were found.

*Comment.*—Clinically and grossly anatomically, this case agreed closely with the criteria advanced by Siwe for the disease defined by him. It was a case of systemic reticuloendothelial disease, without known causation, in a child with enlargement of the spleen, liver and lymphatic glands, progressive anemia of a noncharacteristic type and hemorrhagic diathesis, especially petechial exanthema and localized tumor-like destructions in the skeleton.

The course was somewhat more protracted and the child was a little older than is the rule in Letterer-Siwe disease. It was these divergencies with respect to course and age that induced Siwe and Abt and Denenholz to exclude Schultz, Wermbter and Puhl's case as not belonging to this group of diseases. In my opinion, this was not justifiable.

In the case reported by Schultz, Wermbter and Puhl there were present, it is true, a cranial lesion and exophthalmos, as in Schüller-Christian disease, but the other symptoms, progressive anemia and hemorrhagic diathesis, and the histologic picture did not agree with those of that disease. Anatomically, the presenting feature in this case was a nonlipoid reticuloendotheliosis. The somewhat greater age of the patient in Schultz, Wermbter and Puhl's case, as compared with the majority, cannot by itself constitute a reason for contending that the case does not belong to the same type as those described by Letterer and Siwe.

Foot and Olcott reported the case of a child who became ill at the age of 2¾ years, exactly the same age as Schultz, Wermbter and Puhl's patient. Foot and Olcott's case was classified by Abt and Denenholz as one of Letterer-Siwe disease and correctly, in my opinion. Nor does the more protracted course justify the exclusion of this case, since the course in both Gittin's case 4 and that recorded by Foot and Olcott was of much longer duration.

The first symptom of disease in case 2 was the infiltration in the oral cavity. When this lesion appeared the boy was healthy, apart from a commonplace (judging from its appearance) dermatosis of noninfectious origin that arose at the same time as the process in the oral cavity. With regard to the possible connection between this dermatosis and the reticuloendothelial cutaneous process, the reader is referred to the discussion of case 1.

The disease of the liver, appearing much later, which corresponded to common catarrhal icterus (epidemic hepatitis), cannot, of course, be made responsible for the proliferation of reticulum cells. It seems to me most likely that the systemic reticuloendothelial disease had been complicated by acute hepatitis of the ordinary infectious form, which at that time was rather widely prevalent in the district in which the

boy lived. Perhaps, by lowering the boy's power of resistance, the systemic disease had facilitated his being infected with the virus of hepatitis.

An accentuation of the clinical symptoms of the hepatic disease might also be expected, owing to the intense swelling of the portal lymphatic glands of the liver, which at the postmortem examination was shown capable of preventing the flow of bile from the liver and gallbladder. These lymphatic glands, in turn, were histologically of the same nature as other enlarged glands; that is, they were the seats of a reticuloendothelial proliferation. In this way the systemic reticuloendothelial disease may have given rise to an exacerbation of the symptoms of stasis; perhaps one is not altogether unjustified in contending that the entire hepatic malady may have been due to a biliary stasis, caused by the enlargement of the lymphatic glands in the portal region, with its secondary consequences for the parenchyma of the liver. This may furnish an explanation of the greatly enlarged and icterically colored liver, with its histologic picture of chronic hepatitis, without the necessity of assuming the presence of two different diseases. It should rather be regarded as a remarkable fact that there was no proliferation of reticuloendothelial cells in the parenchyma of the liver.

This was, therefore, a case of systemic reticuloendothelial disease which clinically resembled Letterer-Siwe disease. The absence of a demonstrable infection before the onset of the disease excludes the possibility of a so-called infectious reticuloendotheliosis. There was no clinical evidence for diagnosing the condition in this case as Schüller-Christian disease. Anatomically, however, this disease must be taken into consideration, owing to a storage of lipoids in certain cells. In this case isolated foam cells were found in the skin, the lymphatic glands and the bone marrow, and in somewhat larger numbers in the infiltration in the oral cavity, but on the other hand none were found in the spleen.

It is of course difficult to determine whether the lipoid content in my case was so high as to warrant its being classified histologically as one of Schüller-Christian disease or whether it agrees more with the conditions in certain cases of nonlipoid reticuloendotheliosis. Gellerstedt, the histologist, was of the opinion that the lipoid deposit was not in general remarkably high and that no great etiologic or pathogenetic significance should be ascribed to this lipoidal phagocytosis in some of the cells of the infiltration. Like Rietschel [23] and others, Siwe himself has discussed the possibility of transitional forms between various

23. Rietschel, H., in Nasso, I., and Schwarz, E.: Scritti medici in onore di R. Jemma, Milan, Cromotipia Ettore Sormani, 1934, p. 1093.

pathoanatomic forms of reticuloendotheliosis, particularly between those with and those without lipoid-carrying cells.

Thus, the condition in case 2 agrees clinically with Letterer-Siwe disease; anatomically it occupies, perhaps, an intermediate position between that malady and Schüller-Christian disease.

## COMMENT

An analysis of the symptoms and of the histologic changes in the systemic disease defined as infectious reticuloendotheliosis will show that in these respects there is complete agreement with Letterer-Siwe disease. In the former symptoms of infections complicating the disease are more prominent in certain cases than in Letterer-Siwe disease. The differences between the two diseases are, however, not greater than the clinical variations occurring among cases of either of the diseases.

None of the advocates of the dualistic theory has considered the anatomic foundation to be essentially different in the two diseases. With respect to both the histologic picture and the dissemination of the reticuloendothelial proliferations, the resemblance is complete. The chief anatomic feature in both diseases is an expansive, tumor-like or more diffuse (in the skin) proliferation of reticulum cells or endothelial cells, localized in the thymus, lymphatic glands, liver, spleen and skeletal system but with little or no storage of lipoid in the cells. The differences in the spread, localization and histologic picture of the reticuloendothelial proliferations that may exist between cases of the two diseases are not greater than the variations in pathologic anatomy between different cases of the same disease.

It is difficult to imagine that one of these two rare reticuloendothelial diseases, which agree with each other to such an extent with respect to symptoms, course, age of the patient, histologic picture and dissemination and localization of anatomic changes, is caused by an acute infection of any kind, while the other is of noninfectious origin. One gets a vivid impression that the infection demonstrated in the so-called infectious reticuloendotheliosis has nothing to do with the causation of the disease. Such an opinion finds support in the apparently rather arbitrary and variable manner in which the published cases of the disease are classified. By way of example I may mention that Letterer, Akiba, Podvinec and Terplan, Guizetti and Foot and Olcott have themselves interpreted the conditions in their cases as being due to infection, while Siwe and Abt and Denenholz have classified them as noninfectious reticuloendotheliosis. Even in those cases regarded as instances of noninfectious reticuloendotheliosis there was, in fact, an infection or an infection was suspected; that was true also of Siwe's case (fever) as well as that recorded by Abt and Denenholz (infected nevus, fever). I think it

would be difficult to find a single case of nonlipoid reticuloendotheliosis in which it can be proved for certain that no infection was present.

On the other hand, it is tempting to assume an infectious causation for these reticuloendothelial diseases, since it has been shown that certain infections (tuberculosis, typhoid or malaria) may produce a local proliferation of reticulum cells. But such an infectious proliferation of reticulum cells does not develop into an independent, expansive, infiltrative, progressing, general granulomatosis, as was the case in the reticuloendothelioses under discussion.

If an infection plays a role in the genesis of so-called infectious reticuloendotheliosis, then, in view of the clinical and anatomic identity, an infection should also be the cause of the condition in those cases classified as Letterer-Siwe disease. In that case the infectious agent must be a virus that cannot be cultivated by ordinary methods: In Letterer-Siwe disease no infectious agent could be demonstrated in spite of repeated systematic bacteriologic investigations. It is equally probable, however, that neither disease is of infectious causation and that the infections demonstrated are only accidental complications. Infections of the kind shown to be present in these cases are so exceedingly common in early childhood that their occurrence cannot furnish any support whatever for the assumption that a rare systemic disease which appears during or after such an infection is caused by that infection.

It is conceivable that in such cases the infection may have hastened the outbreak of the systemic disease or aggravated it. But it must also be taken into account that the systemic disease may have begun before the acute infection took place, although it had not yet manifested any symptoms. It may also happen that the reticuloendothelial disease, by lowering the patient's resistance, favors the occurrence of an acute infection or makes such an infection more serious. All kinds of complicating infectious disease may occur to color the clinical picture, especially toward the termination of the disease, when the patient is in poor condition. In this respect this malady certainly does not differ from other malignant diseases, such as acute leukemia, lymphogranulomatosis and malignant tumors.

From what has been said it is clear that the reasons for regarding so-called infectious systemic reticuloendotheliosis and Letterer-Siwe disease as two essentially different maladies are not valid and that all the evidence seems to point to their being identical.

Ever since Christian [24] described the disease that subsequently came to bear his name and that of Schüller,[25] it has been contended that this

24. Christian, H. A., cited by Merritt and Paige.[22]

25. Schüller, A.: Fortschr. a. d. Geb. d. Röntgenstrahlen **23**:12, 1915.

so-called osseous xanthomatosis, or Schüller-Christian disease, was characterized by the following three cardinal clinical symptoms: diabetes insipidus, exophthalmos and lacunar lesions in the calvarial bone. When the characteristic histologic picture of the disease was fully established, especially by the works of Rowland [26] and Epstein,[27] it became increasingly evident that the disease might also appear in an entirely different manner than in association with the aforementioned triad. In many cases all three symptoms were absent and disturbances occurred, instead, in quite different organs. The nature of the symptoms depends, among other things, on the localization of the lesions, and this may vary widely in different cases.

This diversity of the symptomatic pictures induced Henschen to divide Schüller-Christian disease into eight different types characterized by: (1) the aforementioned typical triad (diabetes insipidus, exophthalmos and xanthomatous lesions in the cranial bone), (2) the same symptoms but without diabetes insipidus, (3) the same symptoms as in (1) with the exception of exophthalmos, (4) the same skeletal changes as in (1) but without diabetes insipidus and exophthalmos, (5) the same symptoms as in (1) but with no skeletal changes, (6) xanthomatosis with disturbances of growth, (7) xanthomatosis without any of the symptoms mentioned and (8) xanthomatosis exclusively of the skin.

Even from this classification one gets an idea of the variability of symptoms. In addition to the variation in clinical symptoms there are also great variations in the course of the disease, which is sometimes benign with healing as the ultimate result, and sometimes malignant, leading to death.

The feature common to all these types of disease is the histologic picture with its large numbers of cholesterol-containing foam cells in the granulomas. This storage of cholesterol by the proliferating reticulum cells has been taken by Rowland as the starting point of a hypothesis of the pathogenesis of the disease, which is at present fairly generally accepted. The disease is interpreted as a primary disturbance of the lipoid metabolism and is joined as a third link to the other two known lipoid storage diseases: Gaucher's disease and Niemann-Pick disease. These three diseases are distinguished from one another not only by differences in clinical symptoms and course but also by the nature of the lipoid deposited in the cells: kerasin in Gaucher's disease, phosphatide in Niemann-Pick disease and cholesterol in Schüller-Christian disease.

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26. Rowland, R. S.: Xanthomatosis and Reticulo-Endothelial System: Correlation of Unidentified Group of Cases Described as Defects in Membranous Bones, Exophthalmos and Diabetes Insipidus (Christian's Syndrome), Arch. Int. Med. **42**:611 (Nov.) 1928.

27. Epstein, E.: Ztschr. f. physiol. Chem. **190**:44, 1930; **192**:145, 1930.

Rowland regarded the disorder of the lipoid metabolism as the primary phenomenon and the infiltration of reticulum cells as the secondary phenomenon, caused by irritation and phagocytosis of the abnormal amount of cholesterol supplied by the blood. Other authors, among them Ceelen, Gerstel,[28] Thannhauser and Magendantz and Wätjen, expressed the opinion that the lipoidal deposit in the cells is a secondary and local phenomenon: The reticulum cells, proliferating for some unknown reason, are furnished with strong phagocytic properties and ingest the cholesterol supplied by the blood.

Close study of the published necropsy reports and case histories makes one doubt the correctness of regarding the storage of lipoid in the reticulum cells as essential and usable in distinguishing between Schüller-Christian disease and other reticuloendothelial granulomas. The reason for this skepticism is that while the proliferation of reticulum cells in Schüller-Christian disease shows large numbers of cholesterol-containing foam cells in certain organs, these cells may be absent altogether in the proliferations of reticulum cells in other organs (Kraus and Barth, Grady and Stewart,[29] Merritt and Paige, Wätjen, and others). Thus, since the proliferation of reticulum cells can obviously take place without a trace of any preceding local accumulation of lipoid material in the affected organ, Rowland's view that a disturbance of the cholesterol metabolism is the primary phenomenon can hardly be correct. The deposit of cholesterol in some of these proliferating reticulum cells must be a secondary phenomenon, something that cannot be regarded as pathognomonic of Schüller-Christian disease, as it may be absent in certain of the affected organs. The hypercholesterolemia concomitant with Rowland's theory is certainly not demonstrable in every case of Schüller-Christian disease, and on the other hand it may be present in other cases of reticuloendotheliosis that are not classified as Schüller-Christian disease (van Creveld). In those cases in which hypercholesterolemia is present it may just as well be a secondary phenomenon resulting from the proliferation of reticulum cells.

During the course of the disease the histologic picture varies in the same person. Examinations made at a rather early stage of the disease have shown the presence of a nonlipoid reticuloendotheliosis, while examinations at necropsy have revealed the infiltrations of foam cells typical of Schüller-Christian disease (Flori and Parenti[30]). On the other hand, material removed for biopsy has revealed the presence of Schüller-Christian disease, but when the disease has healed these

28. Gerstel, G.: Virchows Arch. f. path. Anat. **294**:278, 1934.

29. Grady, H. G., and Stewart, H. L.: Hand-Schüller-Christian's Disease and Tuberculosis, Arch. Path. **18**:699 (Nov.) 1934.

30. Flori, A., and Parenti, G. C.: Riv. di clin. pediat. **35**:193, 1937.

typically xanthomatous lesions have been replaced by connective tissue scars without any accumulation of lipoidal material (Merritt and Paige;[22] Sosman[31]).

A close study of the published reports of cases of Schüller-Christian disease with regard to the occurrence of foam cells shows that large numbers of such cells are contained especially in, as far as can be judged, fairly old granulomas and above all in those showing necrosis. On the other hand, foam cells are missing or occur only singly in the more recent proliferations of reticulum cells. From this fact, too, it can be gathered that the storage of lipoid is probably a secondary phenomenon following a reticuloendothelial proliferation that has been going on for some time (a degenerative phenomenon?). If the disease heals the cholesterol is carried away, the necroses are replaced by connective tissue and the final stage is a collagenic scar.

The observations cited here were made by different investigators (Ceelen, Wätjen, Thannhauser and Magendantz and others) and they argue decisively against the view that Schüller-Christian disease is primarily a disease of lipoid metabolism, belonging to the same group of lipoid-storage diseases as Gaucher's disease and Niemann-Pick disease. These observations also argue against the contention that the accumulation of cholesterol in the granulomas is an essential feature of the disease. There is, therefore, no justification in classifying the disease as a xanthomatosis, owing to the fact that xanthoma cells (cholesterol-containing cells) are not found in all the diseased organs and that the xanthomatosis itself appears to be a transient developmental stage of the disease. The abnormality in the deposition of cholesterol, characteristic of certain granulomas, is purely local, and, as already pointed out, hypercholesterolemia is not a condition necessary to the diagonsis.

Thus certain facts indicate that the storage of lipoid in the cells is a secondary, nonobligate phagocytic phenomenon resulting from a reticuloendothelial proliferation that constitutes the essence of the disease. Even this systemic reticuloendothelial disease has been regarded by some authors as the effect of some kind of infection (Thompson, Keegan and Dunn[32]). Against this contention the reasons advanced for the connection between the infection and the reticuloendothelial proliferation in certain cases of nonlipoid reticuloendotheliosis may be repeated almost word for word. The evidence in support of the view that Schüller-Christian disease is due to an infection demonstrable by

31. Sosman, M. C.: Xanthomatosis (Schüller-Christian's Disease; Lipoid Histiocytosis), J. A. M. A. **98**:110 (Jan. 9) 1932.

32. Thompson, C. Q.; Keegan, J. J., and Dunn, A. D.: Defects of Membranous Bones, Exophthalmos and Diabetes Insipidus, Arch. Int. Med. **36**:650 (Nov.) 1925.

available methods is, if possible, still less satisfactory. In the majority of cases there is no indication of any etiologic connection with infection, so that at present the disease is generally regarded as noninfectious. The cause of Schüller-Christian disease is as obscure as that of nonlipoid reticuloendotheliosis; both diseases are systemic reticuloendothelial granulomas of unknown genesis.

From what has been said it appears that the histologic picture of Schüller-Christian disease may be similar to that of Letterer-Siwe disease. Apart from the larger amounts of lipoids stored in certain cells in at least some of the organs involved in the former malady, the two diseases are histologically identical. The organic lesions in which such cholesterol deposits are absent are similar in both diseases, as far as can be judged from the photomicrographs and descriptions in published case reports. Supposing that in a certain case of Schüller-Christian disease foam cells occurred exclusively in a single organ and that that organ was inadvertently not examined, the disease would be interpreted as Letterer-Siwe disease instead. In other words, it may be by mere chance, theoretically at least, that the reticuloendothelial proliferation is classified under the one name or the other.

Now, since infiltration of foam cells can hardly be regarded as an essential and primary feature of Schüller-Christian disease but is rather a secondary phenomenon, the boundary line between Schüller-Christian disease and Letterer-Siwe disease, as far as the anatomic basis is concerned, appears to be eliminated. The absence or presence of cholesterol deposits in the proliferating reticulum cells cannot, at any rate, be the determining factor in classifying the process as one disease or the other. There seem to be many transitional forms between those general xanthomatoses regarded as typical and a reticuloendothelial proliferation with a small number of foam cells or none at all. An instance of this is my case 2. Even in the cases of Letterer-Siwe disease, which are considered to be entirely different pathogenetically, lipoid deposits may, as already pointed out, occur in certain cells (Siwe).

It is clear that, anatomically, there is no distinguishing feature between Schüller-Christian disease and Letterer-Siwe disease. If they are really two different diseases, the course and symptoms at least should always differ to such an extent that the two can be distinguished with their aid. But that does not seem to be the case.

Letterer-Siwe disease is always fatal, whereas it is estimated that about 30 per cent of the patients with Schüller-Christian disease recover. The former malady frequently runs a rather acute course, while the latter is characterized by a protracted, chronic course. Up to the present there has been no exception to the rule that Letterer-Siwe

disease is a malignant disease. On the other hand, there are several exceptions to the rule that Schüller-Christian disease always runs a protracted course; this disease, too, may be rather rapidly fatal.

Evidence has been adduced here indicating that the storage of cholesterol in the proliferating reticulum cells in Schüller-Christian disease is probably a secondary phenomenon following the formation of granulomas. The earlier the anatomic examination the greater should be the probability, under such conditions, that no lipoid deposit is present or that the amount stored is small. In cases in which the disease runs a malignant course and ends fatally within a short time the characteristic xanthoma cells of Schüller-Christian disease should be absent or should be present in smaller numbers than in those cases in which the disease pursues a longer course. That seems, generally speaking, to be true, although exceptions are encountered. One may then ask whether it is not the rapid course of Letterer-Siwe disease that prevents it from progressing far enough to obtain the cholesterol storage in the cells which is typical of Schüller-Christian disease.

If this view is correct, it is possible to understand and explain why Letterer-Siwe and Schüller-Christian diseases may differ so much with respect to course and anatomic picture in spite of their possibly being manifestations of the same malady. The reason a storage of cholesterol is not found in the cases of Letterer-Siwe disease is, therefore, the rapid course of the disease; it is the constant cholesterol deposit in the slowly progressing cases that is the reason foam cells are always found in systemic reticuloendotheliosis with a slow course. If Letterer-Siwe disease and Schüller-Christian disease are identical, which I offer here as a working hypothesis, plausible explanation is obtained of why they are dissimilar anatomically in that foam cells are present in one of them and not in the other, and that the course in one is always malignant while in the other it is usually more benign.

If the two diseases are identical, their clinical manifestations should be similar. A cursory examination of the symptoms in the published case reports will show that this is not the case. The complete, characteristic triad of Schüller-Christian disease, exophthalmos, diabetes insipidus and lesions in the skull, has not occurred in a single one of the cases published or classified as nonlipoid reticuloendotheliosis. Judging from present limited experience, the most common seats of the osseous destructions found in the majority of cases seem to be different in the two types of diseases: the calvarial bones in Schüller-Christian disease and the long bones or the ribs in Letterer-Siwe disease. My case 1, however, illustrates that the localization and spread of the osseous lesions of the reticuloendothelial proliferations in Letterer-Siwe disease may correspond entirely with those in Schüller-Christian disease. In the

case reported by Schultz, Wermbter and Puhl, referred to the group of infectious reticuloendothelioses, there occurred not only osseous defects in the skull but also exophthalmos. On the other hand, not a few cases of Schüller-Christian disease have been recorded in which *Lückenschädel* was absent but lesions were found in the long tubular bones.

The complete, characteristic triad of Schüller-Christian disease is present in only a small number of cases of this disease. As appears from Henschen's account, often only one or two of the symptoms of the triad are present, and not infrequently none of them occur. In other words, the symptoms of Schüller-Christian disease may be quite atypical and in certain cases may differ so completely from those usual in the disease that one may think one is dealing with an entirely different malady.

The symptons regarded as characteristic of Letterer-Siwe disease—progressive anemia, hemorrhagic diathesis, splenic and hepatic enlargement, swelling of the lymphatic glands, fever and frequent osseous lesions—are not foreign to these atypical cases of Schüller-Christian disease. Symptoms are especially atypical in those cases of the latter disease in which the course is more rapid, and in some of these cases the symptoms may coincide exactly with those seen in nonlipoid reticuloendotheliosis. By way of example, a case of Schüller-Christian disease previously reported by Lichty [21] is presented.

LICHTY'S CASE.—A girl aged 21 months was admitted to the hospital in March 1932 with the diagnosis of anemia. She had previously been in good health.

The illness began at the age of 15 months, with a swelling at one of the margins of the lower jaw. Trauma to the left parietal region subsequently resulted in swelling. Her health then became poorer, and she had otorrhea, necessitating mastoidectomy (granulomatous tissue in the middle ear). Shortly afterward there was a spontaneous fracture of the right femur.

Two months before admission progressive anemia, which called for repeated blood transfusions, appeared. There was a seborrheic dermatitis-like eruption. The hemoglobin content was 15 per cent, and the red blood corpuscles numbered 900,000 and the leukocytes 7,000. Xanthoma cells were demonstrated in the puncture of the bone marrow. The liver and spleen were enlarged.

The disease ran a course similar to that of an aplastic anemia, with hemorrhagic diathesis, epistaxis and hemorrhages of the gums. There was no polyuria and no exophthalmos. The child died forty days after admission. Histologic examination showed reticuloendothelial proliferation with infiltration of foam cells.

Similar cases have been described by Flori and Parenti, Gerstel, Klostermeyer,[33] Merritt and Paige, Rietschel, and Sundelius [34] among others. All the patients were infants or young children who had become ill with a dermatosis reminiscent of seborrheic dermatitis, splenic and hepatic enlargement, frequently a swelling of the lymphatic glands,

33. Klostermeyer, W.: Beitr. z. path. Anat. u. z. allg. Path. **93**:1, 1934.
34. Sundelius, H.: Acta med. Scandinav. **87**:402, 1936.

and osseous destructions, followed by fever, progressive anemia of a noncharacteristic type and hemorrhagic diathesis. The disease ran a relatively rapid, fatal course. Positive anatomic proofs were furnished in each case that the condition present was Schüller-Christian disease. The similarity to the symptoms in the cases I have described is striking.

The reason Schüller-Christian disease behaves in this manner only in exceptional cases while this symptomatic picture is characteristic of Letterer-Siwe disease is certainly due to the fact that the former usually

*Cases Classified as Infectious Reticuloendotheliosis, Letterer-Siwe Disease and Schüller-Christian Disease, Arranged According to the Duration of the Disease*

| Author | Year Published | Sex | Age at Onset | Duration | Anemia | Hemorrhagic Diathesis | Enlarged Lymph Gland, Spleen, Liver | Osseous Infiltration | Fever | Anatomic Diagnosis |
|---|---|---|---|---|---|---|---|---|---|---|
| Roussy and Oberling | 1934 | F | 8 mo. | 1 wk. | + | + | + | + | + | L.-S. |
| Podvinec and Terplan | 1931 | ? | 12 mo. | 16 days | + | + | + | — | + | I.R. |
| Uber | 1933 | ? | 21 mo. | 17 days | — | + | + | ? | + | I.R. |
| Guizetti | 1931 | M | 3 mo. | 3 wk. | + | + | + | — | + | L.-S. |
| Gittins (case 2) | 1933 | ? | 21 mo. | 3 wk. | + | + | + | — | + | I.R. |
| Akiba | 1926 | F | 10 mo. | 5 wk. | + | + | + | — | + | L.-S. |
| Klostermeyer | 1934 | F | 13 mo. | 7 wk. | + | — | + | + | + | I.R. |
| van Creveld and ter Poorten | 1935 | F | 4½ mo. | 2 mo. | Hb. 57% | — | + | + | + | I.R. |
| Letterer | 1924 | M | 6 mo. | 2½ mo. | — | + | + | — | + | L.-S. |
| Siwe | 1933 | F | 16 mo. | 3 mo. | + | + | + | + | + | L.-S. |
| Wallgren (case 1) | 1940 | F | 4 mo. | 3 mo. | + | + | + | + | + | L.-S. |
| Wätjen | 1935 | ? | 10 mo. | 3 mo. | ? | ? | + | — | + | S.-C. |
| Rietschel | 1932 | M | 12 mo. | 4 mo. | ? | + | + | + | + | S.-C. |
| Gittins (case 4) | 1933 | ? | 17 wk. | 4 mo. | + | + | + | — | + | L.-S. |
| Abt and Denenholz | 1936 | M | 2 yr. | 4½ mo. | + | + | + | + | + | L.-S. |
| Schultz, Wermbter and Puhl | 1924 | F | 2¾ yr. | 6 mo. | + | + | + | + | + | I.R. |
| Krahn | 1926 | F | 5 yr. | 6 mo. | + | + | + | — | + | I.R. |
| Gerstel | 1934 | F | 26 mo. | 6 mo. | + | + | + | + | + | S.-C. |
| Lichty | 1934 | F | 21 mo. | 7 mo. | + | + | + | + | + | S.-C. |
| Foot and Olcott | 1934 | F | 2¾ yr. | 12 mo. | ? | + | + | + | + | I.R. |
| Wallgren (case 2) | 1940 | M | 26 mo. | 12 mo. | + | + | + | + | + | L.-S.? |
| Flori and Parenti | 1937 | ? | 8 mo. | 18 mo. | + | + | + | + | + | S.-C. |
| Merritt and Paige | 1933 | M | 3 yr. | 24 mo. | + | + | + | + | + | S.-C. |

runs a slow course and the latter a more rapid course; this implies that not only the symptoms but also the pathoanatomic changes may be dissimilar. The accompanying table gives a list, arranged according to the duration of the disease, of the published cases of infectious, general reticuloendotheliosis, Letterer-Siwe disease and some cases of Schüller-Christian disease which clinically resembled cases of nonlipoid endotheliosis. The table shows that the more rapid the course of the disease the less frequently does it resemble, histologically, Schüller-Christian disease. Infiltrations of foam cells occurred only in those cases in which the disease was of three months' or more duration. On the other hand, infiltrations of foam cells were always found if the disease lasted more than twelve months.

The differences are, of course, also due to the different localization of the morbid changes in the different cases. That the course of the disease varies so widely may be due, partly at least, to the fact that Letterer-Siwe disease attacks infants and young children exclusively, while Schüller-Christian disease typically affects somewhat older children and adults. Those cases of Schüller-Christian disease which clinically resembled Letterer-Siwe disease were in infants or young children.

Thus, also as regards the clinical symptoms there need not be any essential difference between Schüller-Christian disease and Letterer-Siwe disease. The differences existing may be satisfactorily explained by the different ages of the patients and by the more rapid or slower courses of the disease. There are many transitional types from one disease to the other. It is not always possible by means of the clinical features alone to distinguish them, and even anatomically it may sometimes be a matter of inclination how the disease is classified.

I consider that I have produced evidence to show that the patho-anatomic bases of Schüller-Christian disease and Letterer-Siwe disease are not incompatible with the assumption that they are the same disease and that the clinical symptoms do not differ to such an extent that they cannot be fully explained by the difference in age of the patients, the varying course of the disease and the different localization and distribution of the granulomas. Neither of the diseases has any characteristic feature that cannot occur in the other. It should be considered whether the present dualistic conception is correct, and new efforts should be made to find out whether the two diseases are etiologically and pathogenetically identical.

## CONCLUSIONS

Reasons have been put forward in support of the view that nonlipoid reticuloendotheliosis and Schüller-Christian disease are identical and that so-called infectious reticuloendotheliosis, Letterer-Siwe disease and Schüller-Christian disease are different types of the same malady.

The essential feature of the disease is a granuloma-like proliferation of the cells of the reticuloendothelial system, which occurs for some unknown reason. If the proliferation takes place in infants or in young children the disease usually runs a relatively malignant course, the predominating symptoms being as a rule those of hemorrhagic diathesis and progressive anemia. In these cases the anatomic picture is generally characterized by a proliferation of reticulum cells in several internal organs and in the skeleton, particularly in the lymphatic glands, the thymus, the spleen, the liver and the bone marrow, with hemorrhages in the involved tissue. In some of these cases the phagocytic properties of the reticulum cells are shown by their ingestion of lipoid, and in

exceptional cases some cells, particularly where there was necrosis, may be changed into cholesterol-containing foam cells.

When the disease occurs in older persons it usually runs a more protracted course, the granulomas appear more like tumorous metastases and the localization of the proliferation of reticulum cells determines the symptoms. In older children and adults there is a certain predisposition for the calvarium, mesencephalon and orbits, irrespective of the dissemination of the lymphatic glands, thymus and other internal organs. Thanks to a more protracted course, the proliferating reticulum cells have sufficient time to ingest a large amount of cholesterol, and in certain places these foam cells greatly exceed the nonvacuolated reticulum cells. In some cases in adults with a prolonged, more benign course the proliferation of reticulum cells gradually ceases, the infiltrates are resorbed, necroses are replaced by scar tissue and the disease heals.

SUMMARY

A description is given of 2 clinically and anatomically investigated cases of systemic reticuloendothelial granuloma, the patients being 4 months and 2½ years of age, respectively. These cases, which essentially show great similarities, occupy intermediate positions, one of them between so-called infectious reticuloendotheliosis and Letterer-Siwe disease and the other between the latter malady and Schüller-Christian disease.

These three types of systemic reticuloendotheliasis, hitherto regarded as different diseases, are discussed and reasons are advanced to show that the distinguishing features between the two first mentioned are rather arbitrary and nonessential and that the anatomic and clinical dissimilarities that may exist between nonlipoid reticuloendotheliosis and Schüller-Christian disease are easily explained by the difference in age of the patients, the unequally malignant or benign course, mainly due to this difference in age, and the different localization of the morbid changes. Transitional types are found between characteristic cases of Schüller-Christian disease and Letterer-Siwe disease and also between those of the latter and so-called infectious reticuloendotheliosis.

# SCHILLING BLOOD COUNT IN JUVENILE LOBAR PNEUMONIA TREATED WITH SULFAPYRIDINE

PRELIMINARY REPORT

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A study of the Schilling blood counts of a series of children ill with various acute infections disclosed that this form of differential smear is extremely significant in interpreting the clinical progress of the underlying pathologic conditions.[1] Thus, when repeated at frequent intervals during the course of an acute infection, this count was shown to anticipate the appearance of a complication, improvement or other change twenty-four hours or more in advance of its appearance clinically.

Shortly after that study a similar one was made in which the examination of the blood smear was limited to cases of acute pneumonia in the young.[2] Among these were 31 cases of lobar pneumonia. Daily changes in the differential count were noted with special reference to the immature granulocytes present. It was observed that the percentage of these nonfilamented, "band" forms was markedly increased during the height of the fever and that a sudden decrease in these elements preceded the crisis in cases of untreated lobar pneumonia by many hours. Thus a definite relation was established between beginning resolution, the fall in temperature and the immature, polymorphonuclear cells of the blood, the underlying pathologic change being reflected in the blood even before clinical improvement occurred.

Since then there have been many opportunities to verify this observation, and it has been possible to construct a characteristic curve representing the nonfilamented granulocytes in the daily blood picture of patients with untreated lobar pneumonia (chart 1). Thus my original observations describing the prognostic value of the differential smear were further confirmed.

With the discovery of sulfapyridine and its remarkable therapeutic effect in lobar pneumonia it became interesting to know precisely how the leukocytes in the peripheral blood responded to this therapy and

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1. Rogatz, J. L.: The Schilling Blood Count in the Prognosis of Acute Infections in Infancy and Childhood, Am. J. Dis. Child. **40**:70 (July) 1930.

2. Rogatz, J. L.: The Schilling Blood Count in the Pneumonias of Infancy and Childhood, Am. J. Dis. Child. **45**:1022 (May) 1933.

whether the dramatic fall in temperature and the clinical improvement were reflected in the blood smear. The question arose as to whether or not the artificially induced crisis was accompanied by corresponding alterations in the underlying pathologic process. Was consolidation interrupted and resolution hastened? Did the sudden drop in temperature following administration of the drug imply that active infection was over as well, or was the effect of the medication merely antipyretic and possibly bacteriostatic?

Since the percentage of immature granulocytes in the blood has been found to be a reliable index of acute infection in the body, it was felt that a further study of these cells might give some additional clue as to the precise nature of the effect of sulfapyridine in pneumonia. Though the present series of cases is small, the results have been constant, and it is felt that since it will take months to accumulate enough cases for a complete study present interest in the mode of action of sulfapyridine justifies the preliminary announcement of any observations which may clarify the problem. No other studies of this nature have been reported thus far.

## PROCEDURE

Roentgenograms, blood cultures and pneumococcus typings were done in all cases and have been reported in a separate study by Leopold and Sobel.[3] Of these, only classic cases of lobar pneumonia were chosen for study of the Schilling smear. Complete blood counts were made on admission and were followed by daily examinations of the differential smear. Total white cell counts were not made after the first day, because it has been found throughout the various studies that they vary greatly during the period of an infection and that they seem to bear no significant relation to the course of the illness. The smears were stained with Wright's stain and examined with special reference to the percentage of immature, polymorphonuclear leukocytes present—a now familiar procedure in routine examinations of the blood.

## OBSERVATIONS

With the first examinations it became apparent that a fall in temperature following the administration of sulfapyridine, regardless of how early in the illness it occurred, was not accompanied by a corresponding reflection of improvement in the differential smear, ordinarily indicated by a sudden decrease in the nonfilamented or immature granulocytes. It was further noted that the first decrease in these cells occurred on the fifth to the seventh day of the illness and that further improvement in the blood proceeded gradually, reaching normal about the tenth to

3. Leopold, J. S., and Sobel, I. P.: Sulfapyridine Therapy in the Pneumonias of Infancy and Childhood, Arch. Pediat. **56**:581 (Sept.) 1939.

the fourteenth day after onset. In other words, the blood picture in sulfapyridine-treated pneumonia was precisely that which we have found repeatedly in untreated pneumonia.

In chart 1 the typical curves for the nonfilamented polymorphonuclear leukocytes in sulfapyridine-treated and in untreated lobar pneumonia have been diagrammatically plotted against a characteristic temperature curve for each of these conditions. It will be noted that in untreated lobar pneumonia the first improvement in the blood occurs just prior to the crisis; in pneumonia treated with sulfapyridine the improvement in the blood occurs after the artificially induced crisis. When the decrease in the immature white cells and the fall in temperature occur

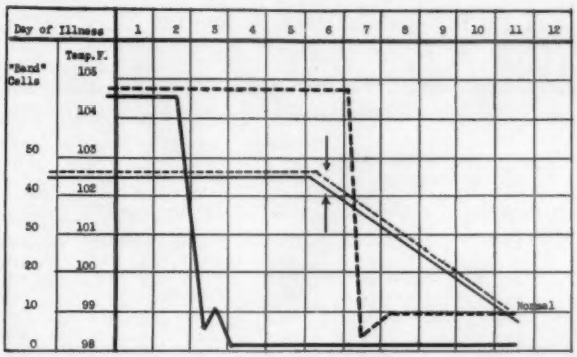


Chart 1.—Diagrammatic curves for immature, polymorphonuclear leukocytes (nonfilamented or "band" cells) plotted against the temperature curves of patients with treated and untreated lobar pneumonia. The dotted lines represent the blood and temperature readings in untreated pneumonia; the solid lines represent those in sulfapyridine-treated pneumonia. The arrows indicate the first improvement in the blood. Note the similarity of the blood curve in the two forms of pneumonia.

simultaneously as in cases 2 and 9, in which the patients were treated late in their illness, the indication is that the artificial crisis occurred at about the time of expected, natural crisis and that the improvement could not be attributed solely to the drug. It was not always possible to get an accurate history of the day of onset, but since repeated observations have proved the constant nature of the blood curve in untreated pneumonia, it was possible to predicate the probable day of the illness from the relation between the fall in temperature and the improvement in the blood, assuming that the crisis in the average lobar pneumonia occurs between the fifth and the seventh day.

Since all patients presented similar findings, the significant data are presented in table 1. A short comment is made on each of the cases. The hemograms and temperature curves in cases 10 and 11 are given in detail as examples of typical findings.

REPORT OF CASES

CASE 1.—E. M., a girl 1 year old, was admitted to the hospital with fever and cough of five days' duration. She had pneumonia in the lower lobe of the left lung. Sulfapyridine was given, and the temperature fell to normal within thirty-six hours. The blood showed 50 per cent immature white cells, a value which fell to 40 per cent on the seventh day of the illness and to 34 per cent on the following day, at about the time the temperature reached 99 F.

Thus the improvement in the blood and the fall in temperature occurring simultaneously suggested that the natural crisis would have occurred at this time had the child not been given the drug. This opinion was borne out by the fact that the sulfapyridine was administered late in the disease. Several days later acute otitis media developed, and further counts were discontinued. However, the case

TABLE 1.—*Analysis of 11 Cases of Lobar Pneumonia in Children*

| Case No. | Age, Years | Location of Pneumonia | | Temperature on Admission, F. | Day of Illness on Which Sulfapyridine Was Given | Day of Crisis | Day of First Improvement in Blood | Day Blood Was Normal |
|---|---|---|---|---|---|---|---|---|
| | | Lung | Lobe | | | | | |
| 1 | 1 | Left | Lower | 105.0 | 5th | 6th | 7th | .... |
| 2 | 6 | Right | Upper | 104.8 | 4th | 7th | 7th | .... |
| 3 | 3 | Right | Lower | 104.0 | 2d | 3d | 4th | 7th |
| 4 | 2½ | Left | Lower | 104.8 | 2d | 3d | 5th | 7th |
| 5 | 11 | Right | Middle | 104.0 | 3d | 4th | 4th | 6th |
| 6 | 9½ | Right | Lower | 105.2 | 3d | 4th | 5th | 10th |
| 7 | 9 mo. | Right | Lower | 104.6 | 6th | 7th | 9th | 20th |
| 8 | 5½ | Right | Upper | 103.4 | 2d | 4th | 5th | 10th |
| 9 | 2 | Left | Lower | 105.0 | 4th | 5th | 5th | 8th |
| 10 | 6 | Right | Upper | 104.0 | 4th | 5th | 7th | 10th |
| 11 | 5½ | Left | Lower | 103.0 | 4th | 5th | 8th | 16th |

does serve to illustrate that a crisis occurring after the late administration of sulfapyridine may be in part natural and not entirely or at all due to the drug.

CASE 2.—R. M., a boy aged 6 years, was admitted to the hospital with cough and fever of four days' duration and pneumonia of the upper lobe of the right lung. The response to sulfapyridine was late, the temperature reaching normal three days after its administration, on the seventh day. At the same time the blood showed its first improvement, the percentage of immature cells falling from 59 to 45.

Here again the final fall in temperature must be considered part of a normal process, rather than due to the drug.

CASE 3.—F. S., a boy aged 3 years, had cough and fever for one day. Sulfapyridine was given on the second day, and the temperature fell abruptly to normal within twenty-four hours. The proportion of immature cells fell from 50 to 32 per cent on the following day, remaining at this level for several days despite a normal temperature and gradually reaching normal on the seventh day.

The course here may be considered somewhat shorter than usual.

CASE 4.—J. C., a boy aged 2½ years, had a history of fever and cough present for two days. He had pneumonia of the lower lobe of the right lung. The immature cell count at the height of the fever (104.8 F.) was 22 per cent, not very high compared with the counts of other cases. The temperature fell to normal within one day after the use of sulfapyridine. First improvement in the blood occurred two days later, on the fifth day of the illness.

The change in the blood would have happened at the same time if the patient had been untreated.

CASE 5.—R. M., a girl aged 11 years, had an indefinite history of about three days of cough and fever. She had pneumonia of the middle lobe of the right lung. She was given the drug on the third day, and the temperature fell on the fourth day simultaneously with a drop in the immature cell count from 43 to 20 per cent.

Here again the simultaneous occurrence of improvement in the temperature and in the blood suggest some inaccuracy in the history, the child in all probability having been ill more than three days.

CASE 6.—J. S., a boy aged 9½ years was given sulfapyridine on the third day of his illness, the temperature reaching normal on the fourth day. The percentage of immature cells in the blood fell from 45 to 27 on the fifth day, gradually reaching normal on the tenth day.

This patient presented the typical picture of untreated pneumonia despite the administration of the drug and consequent clinical improvement.

CASE 7.—R. A., a Negro boy 9 months old, was admitted to the hospital with a history of fever for five days. He had pneumonia in the lower lobe of the right lung. His total white cell count was 23,000 per cubic millimeter, and he had a temperature of 104.6 F. The temperature fell to normal after two days of treatment with sulfapyridine. The significant part of the differential count showed 40 per cent immature cells on the day of admission, 48 per cent on the following day and 49 per cent on the third day after the administration of the drug. After forty-eight hours of normal temperature the count of the immature cells fell to 28 per cent. During the ensuing week the temperature remained normal, but the immature cells rose to about 40 per cent and remained at this level during twelve days of normal temperature. The blood finally approached normal on the twentieth day of the illness.

A doubtful history makes it difficult for one to know precisely on what day of the pneumonia the patient was admitted. The lag in the improvement in the blood after administration of the drug makes it highly probable that the pneumonia was not of more than three days' duration on the patient's admission. Of even greater interest are the slow return of the blood to normal after the sulfapyridine had taken effect and the prolongation of convalescence.

CASE 8.—R. H., a 5½ year old boy, was admitted to the hospital with a history of cough and fever of two days' duration. He had pneumonia in the upper lobe of

the right lung. The temperature fell to normal after two days of treatment with sulfapyridine, on the fourth day of the illness. On the following day the blood showed the first sign of improvement, when the immature cell count fell from 47 to 28 per cent. The blood count continued at this approximate level for several days, first approaching normal on the tenth day, after which it was necessary to discontinue the counts.

CASE 9.—F. F., a 2 year old boy, was ill three days with fever and cough. He had pneumonia of the lower lobe of the left lung. The temperature fell to normal

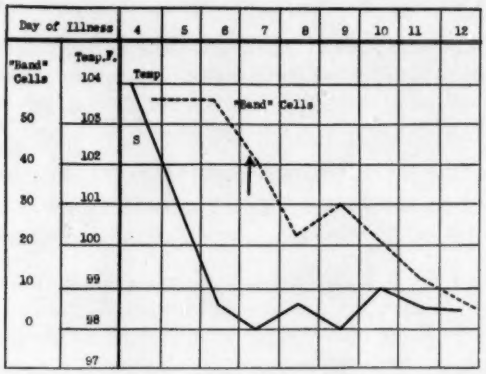


Chart 2.—Curves showing the percentage of "band" cells and the course of the temperature of the patient in case 10. Note the arrow indicating the first improvement in the blood, two days after the crisis induced by sulfapyridine. Note also the slow return to normal.

TABLE 2.—*Hemogram of the Patient in Case 10*

| Date | Temperature, F. | Basophils | Eosinophils | Immature (Nonfilament) Polymorphonuclears | Segments (Mature) | Lymphocytes | Monocytes |
|---|---|---|---|---|---|---|---|
| 10/2/39 | 104.0 | .. | .. | 64 | 14 | 20 | 2 |
| 10/3/39 | 101.0 | 1 | .. | 64 | 16 | 13 | 6 |
| 10/4/39 | 98.6 | .. | 4 | 61 | 14 | 16 | 5 |
| 10/5/39 | 98.0 | .. | 5 | 44 | 7 | 38 | 6 |
| 10/6/39 | 98.6 | .. | 5 | 23 | 7 | 56 | 9 |
| 10/7/39 | 98.0 | 1 | 4 | 30 | 24 | 34 | 7 |
| 10/8/39 | 99.0 | 2 | 4 | 22 | 15 | 47 | 10 |
| 10/9/39 | 99.0 | .. | .. | 13 | 22 | 61 | 4 |

after one day of sulfapyridine, and the immature cell count decreased from 40 to 29 per cent at the same time, on what appeared to be the fifth day of the illness. The percentage of immature cells was normal on the eighth day of the illness.

CASE 10.—T. D., a 6 year old boy, had fever and cough for three days before admission. He had pneumonia of the upper lobe of the right lung. His temperature was 104 F., and his total white cell count was 14,000 cells per cubic millimeter, with 64 per cent of immature forms at the height of his illness. Sulfapyridine was administered, and the temperature fell to normal between the fifth and the sixth day, improvement in the blood first occurring twenty-four hours later when the

immature cell count fell from 61 to 44 per cent. There was continued gradual improvement in the blood, which appeared normal ten days after the onset of the pneumonia, six days after the drop in temperature following the administration of sulfapyridine (table 2 and chart 2).

CASE 11.—M. P., a 5½ year old girl, was admitted to the hospital with a history of cough and fever for three days. Her temperature was 103 F. She had 26,000 leukocytes per cubic millimeter in her blood. Physical signs and a roentgenogram

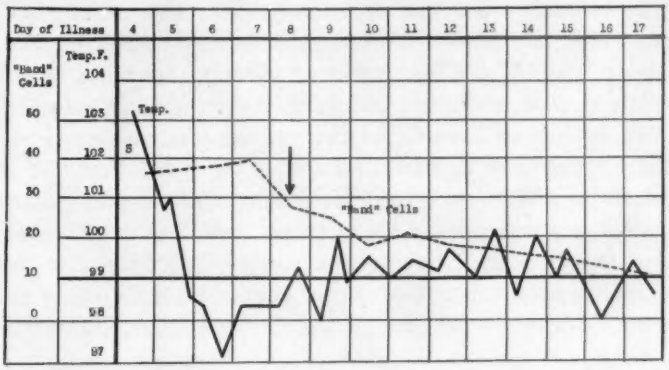


Chart 3.—Curve showing the percentage of "band" cells and the course of the temperature of the patient in case 11. The arrow indicates the first improvement in the blood, three days after the crisis which followed administration of sulfapyridine. Note also the slow return to normal.

TABLE 3.—*Hemogram of the Patient in Case 11*

| Date | Temperature, F. | Basophils | Eosinophils | Immature (Nonfilament) Polymorphonuclears | Segments (Mature) | Lymphocytes | Monocytes |
|---|---|---|---|---|---|---|---|
| 11/11/39 | 103.0 | .. | .. | 46 | 46 | 8 | .. |
| 11/13/39 | 98.6 | .. | 1 | 50 | 10 | 30 | 9 |
| 11/14/39 | 98.6 | .. | 1 | 53 | 6 | 36 | 4 |
| 11/15/39 | 98.0 | .. | 2 | 37 | 19 | 33 | 9 |
| 11/16/39 | 100.0 | .. | 2 | 34 | 22 | 32 | 10 |
| 11/17/39 | 99.0 | .. | 1 | 27 | 19 | 48 | 5 |
| 11/18/29 | 99.6 | .. | 3 | 33 | 34 | 27 | 3 |
| 11/19/39 | 100.0 | .. | 1 | 27 | 23 | 45 | 4 |
| 11/20/39 | 99.0 | .. | 1 | 25 | 23 | 48 | 3 |
| 11/22/39 | 99.6 | 3 | .. | 16 | 28 | 48 | 3 |
| 11/24/39 | 99.0 | .. | 4 | 16 | 30 | 47 | 3 |

of the chest showed pneumonia in the lower lobe of the left lung. The immature cell count was 46 per cent. The temperature fell to normal within thirty-six hours after the first dose of sulfapyridine, but the first improvement in the blood occurred three days later when the immature cell count fell from 53 to 37 per cent. Slow improvement in the blood continued while the temperature remained normal. The blood first approached normal on the sixteenth day of the illness, eleven days after clinical improvement following the administration of sulfapyridine (table 3 and chart 3).

## COMMENT

I cannot agree with Smith and Nemir,[4] who concluded from their recent studies of lobar pneumonia that the disease is not only interrupted clinically by the use of sulfapyridine but that resolution is also hastened and occurs more rapidly than when the disease is untreated. Their examinations did not include serial examinations of the blood, which give evidence to the contrary. Thus, if there were a concomitant resolution following the use of sulfapyridine, the differential count, being an extremely sensitive indicator of acute, pathologic alterations in the body, should give immediate information. As has been shown, this does not occur, the blood picture in the treated patients being precisely that which we have found in the untreated patients.

This fact may also be used to disprove the contention of many that the remarkable effectiveness of sulfapyridine may in part be attributed to the possibility that pneumonia in recent years has not been as severe as that of earlier years. The present studies indicate clearly that cases of lobar pneumonia still run a typical course with the crisis occurring on the fifth to the seventh day of the illness in most instances.

## CONCLUSIONS

There is a constant relation between a natural crisis and the decrease in the nonfilamented, polymorphonuclear leukocytes of the blood in lobar pneumonia which does not appear in the artificial crises induced by sulfapyridine. These studies suggest that the pathologic course of lobar pneumonia is not greatly altered by the use of sulfapyridine and that, despite the obvious clinical improvement and the fall in temperature, the immature granulocytes of the blood do not reflect this improvement but rather indicate a continuation of the familiar process of hepatization and resolution which characterizes the course of the untreated patient. The practical application is clear. It is wise to continue convalescence, as with the untreated patient, at least until the blood smear has returned to normal.

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4. Smith, C. H., and Nemir, R. L.: The Sulfapyridine Treatment of Pneumonia in Children, J. A. M. A. **113**:1857 (Nov. 18) 1939.

# EFFECT OF VARIED BANANA INTAKE ON NITROGEN AND MINERAL BALANCES OF NORMAL CHILDREN

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DETROIT

The nutritive advantage of supplementary banana in the diets of children has been demonstrated. Roberts and her co-workers [1] have shown that in an institution 123 boys whose diet was supplemented with two or three bananas daily over a nine month period made a slightly greater mean gain in weight and height than a control group; they also showed slightly greater progress in ossification of the bones of the wrist and greater mean gains in measurements of arm girth, subcutaneous tissue and weight (Franzen measurements) and also in the scores for these items. These authors emphasized that the differences did not in most cases attain statistical significance, but because the investigation was made on matched groups and the results were consistent in direction they expressed the belief that the differences were real ones attributable to the supplement. The nutritive advantage of the banana has been attributed to its excess alkaline-ash value,[2] to special physiologic properties of its

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Alfred T. Shohl, M.D., gave assistance in the standardization of terminology relating to acid-base metabolism, prior to publication of his monograph on mineral metabolism.

1. Roberts, L. J.; Blair, R.; Austin, G., and Steininger, G.: The Supplementary Value of the Banana in Institution Diets: I. Effect on Growth in Height and Weight, Ossification of Carpals, and Changes in Franzen Indices, J. Pediat. **15**:25, 1939.

2. Macy, I. G.; Hummel, F. C.; Hunscher, H. A.; Shepherd, M. L., and Souders, H. J.: Effects of Simple Dietary Alterations upon Retention of Positive and Negative Minerals by Children, J. Nutrition **19**:461, 1940.

unavailable carbohydrate content and their effect on digestion, absorption and elimination [3] and to its improvement of the storage of vitamin C, measured by capillary resistance and reduced content of ascorbic acid in the blood plasma.[4]

The wide differences in response of human subjects have been emphasized, and because of the uncontrollable factors (heredity, previous health, nutritive state and emotional status) we have emphasized the importance of having each experimental subject serve as his own control in metabolic investigations. The intensity of response may depend on the stage or phase of growth of the person at a given time; consequently, it is exceedingly important to extend observations over intervals sufficient to minimize these and other temporary individual effects.[5] If the metabolic balances are determined over a number of consecutive periods, the uncontrollable factors are minimized. Reasonably well filled body stores may be assured in the subjects by controlled feeding during two or three months preceding the experimental period, and the subjects can be further prepared for study by two or three weeks' training in the metabolic routine of consuming all the food given and separating the urine from the feces. The chemical analyses must be made with methods of greatest precision and by experienced and trained chemists. Under these conditions confidence in the reliability of the data secured is warranted.

In the present study of the effects of incorporating 100 or 200 Gm. of banana per day in the diets of 8 average, healthy children, the subjects were selected for their excellent health records,[6] amenable personalities and skeletal development [7] comparable with their chrono-

3. (*a*) Hummel, F. C.; Shepherd, M. L., and Macy, I. G.: Effect of Changes in Food Intakes upon the Lignin, Cellulose, and Hemicellulose Contents of Diets, Am. J. Dietetics **16**:199, 1940. (*b*) Shepherd, M. L.; Hummel, F. C., and Macy, I. G.: Influence of Raw Banana and Apple upon Disappearance of Complex Carbohydrates from the Alimentary Tracts of Normal Children, Am. J. Digest. Dis. **7**:248, 1940.

4. Roberts, L. J.; Brooks, M. H.; Blair, R.; Austin, G., and Noble, I.: The Supplementary Value of the Banana in Institution Diets: II. Capillary Resistance and Reduced Ascorbic Acid in the Blood Plasma, J. Pediat. **15**:43, 1939.

5. Hummel, F. C.; Hunscher, H. A., and Macy, I. G.: Effect of Irradiated Milks on Storage of Nitrogen and Acid-Base Minerals in Children, Am. J. Dis. Child. **58**:753 (Oct.) 1939. Souders, H. J.; Hunscher, H. A.; Hummel, F. C., and Macy, I. G.: Influence of Fluid and of Evaporated Milk on Mineral and Nitrogen Metabolism of Growing Children, ibid. **58**:529 (Sept.) 1939.

6. Marsh W. Poole, M.D., attending physician at the Methodist Children's Village, made the medical examinations and the physical measurements of the children.

7. The late T. Wingate Todd, M.D., and C. C. Francis, M.D., Western Reserve University, evaluated and studied the skeletal maturity of the children.

logic ages. The youngsters, 5 to 8 years of age, experienced three months of preliminary feeding and at least two weeks' training in metabolic technic; they lived in an environment that stimulated normal, happy, healthful living; the metabolic balances were run continuously, with the control periods preceding experimental periods of similar duration; each child was observed for from fifty to ninety consecutive days; and no test interval was shorter than twenty days, the majority being thirty to forty-five days in length. The extent of the data procured from study of the balances of nitrogen and the acid-base minerals (calcium, magnesium, sodium, potassium, phosphorus, sulfur and chlorine) prohibits detailed publication in this paper, and since preceding papers [8] have shown that the banana produced specific trends in the metabolism of the subjects, the data for the 8 children have been combined for the preexperimental period totaling two hundred and seventy-five days and for the experimental period of two hundred and eighty-five days. The individual values for each five day balance period will be included in a monograph being prepared on the chemical growth and nutrition of children.

## RESULTS AND COMMENT

Potentially alkaline diets have been shown to improve nitrogen storage in children [9] and in dogs [10] but to have little effect on the retentions of calcium and phosphorus. Furthermore, ingestion of ascorbic acid has been shown to influence the retention of nitrogen more than the accumulation of calcium, magnesium or phosphorus.[11] By increasing the banana intake the ascorbic acid intake is increased by approximately 15 mg. for each 100 Gm. of banana. This quantity of ascorbic acid might have an appreciable effect on metabolism if the subject possessed an inadequate storage or should the intake of ascorbic acid be below the physiologic minimum. The children of the present study received during the preexperimental period from 53 to 89 mg. of ascorbic acid daily (2.6 to 4.9 mg. per kilogram of body weight [4]) and during the experimental period with the supplement of banana the daily intakes ranged from 68 to 104 mg. (3.2 to 5.9 mg. per kilogram of body weight).

8. Macy, Hummel, Hunscher, Shepherd and Souders.[2] Hummel, Shepherd and Macy.[3]

9. Davis, N. J.: Calcium, Phosphorus and Nitrogen Retention of Children: Effects of Acid-Forming and Base-Forming Diets, Am. J. Dis. Child. **49**:611 (March) 1935.

10. Morgan, A. F.: The Effect of Acid, Neutral, and Basic Diets on the Calcium and Phosphorus Metabolism of Dogs, Univ. California Publ., Physiol. (no. 7) **8**:61, 1934.

11. Baumann, L., and Howard, C. P.: Metabolism of Scurvy in an Adult, Arch. Int. Med. **9**:655 (June) 1912. Daniels, A. L., and Everson, G. J.: The Relation of Ascorbic Acid Ingestion to Mineral Metabolism in Children, J. Nutrition **14**:317, 1937.

This quantity is above that found necessary to prevent even the most minute signs of scurvy in infants studied in this laboratory [12] and is less than the 7.5 mg. per kilogram per day suggested by Everson and Daniels [13] to be the minimum daily amount necessary for young children. The fat excretion in the feces was unchanged by the feeding of one or two bananas per day; [14] consequently, the improved metabolism of the children during periods of increased banana intake cannot be ascribed to this phase of metabolism.

The principal nonvolatile organic acid of the ripe banana is l-malic acid,[15] which constitutes approximately 0.314 per cent of the fruit at the stage of ripeness at which it is usually eaten; the titrable acidity value of ripe banana is about 4.8 cc. of normal alkali per hundred grams.[15] The nutritional and metabolic significance of l-malic acid is not fully

TABLE 1.—*Intake of Apple and Banana of Eight Normal Children During Preexperimental and Experimental Periods*

| | Ingested During Preexperimental Period | | Changes in Diet During Experimental Period | | | |
|---|---|---|---|---|---|---|
| | | | Addition | | Deletion | |
| | Apple, Gm. | Banana, Gm. | Food | Gm. | Food | Gm. |
| Group 1 (3 children) | 100 | 100 | Banana | 100 | None | |
| Group 2 (3 children) | 100 | 100 | Banana | 100 | White bread<br>Cereal* | 10<br>20 |
| Group 3 (2 children) | 200 | None | Banana | 100 | White bread<br>Cereal* | 10<br>20 |

* Shredded wheat or corn flakes.

understood, but experimental work indicates that it stimulates excretion of citric acid and serves as an endogenous precursor of citric acid, which is considered a "physiologic metabolite." [16]

The quantities of apple and banana included in the children's daily diets during the preexperimental period (two hundred and seventy-five days) and the alterations made during the experimental period (two hundred and eighty-five days) in which the effect was studied of incorporating an additional 100 Gm. of banana per day in a general mixed

12. Hamil, B. M.; Reynolds, L.; Poole, M. W., and Macy, I. G.: Minimal Vitamin C Requirements of Artificially Fed Infants: A Study of Four Hundred and Twenty-Seven Children Under a Controlled Dietary Regimen, Am. J. Dis. Child. **56**:561 (Sept.) 1938.

13. Everson, G. J., and Daniels, A. L.: Vitamin C Studies with Children of Preschool Age, J. Nutrition **12**:15, 1936.

14. Unpublished data.

15. Harris, P. L., and Poland, G. L.: Organic Acids of the Ripe Banana, Food Research **2**:135, 1937.

16. Orten, J. M., and Smith, A. H.: A Study of Certain Metabolites and Related Compounds as Precursors of Endogenous Citric Acid, J. Biol. Chem. **117**:555, 1937.

diet [17] are shown in table 1. The intake, excretion and apparent retention of nitrogen, the seven acid-base mineral elements, mineral cations and anions per kilogram of body weight of the 8 subjects are shown in

TABLE 2.—*Nitrogen and Acid-Base Mineral Balances Per Kilogram of Body Weight of Eight Children During a Preexperimental Period of Two Hundred and Seventy-Five Days and Experimental Period of Two Hundred and Eighty-Five Days* *

| | | Excretion | | | | Apparent Retention † | |
|---|---|---|---|---|---|---|---|
| | | Urine | | Feces | | | |
| | Intake, Average | Average | Per Cent of Intake | Average | Per Cent of Intake | Average | Per Cent of Intake |
| Nitrogen (mg.) | | | | | | | |
| Preexperimental | 506 | 436 | 86 | 53 | 11 | 17 | 3 |
| Experimental | 489 | 416 | 85 | 51 | 11 | 22 | 4 |
| Calcium (mg.) | | | | | | | |
| Preexperimental | 38 | 5 | 13 | 29 | 76 | 4 | 11 |
| Experimental | 37 | 4 | 11 | 28 | 75 | 5 | 14 |
| Magnesium (mg.) | | | | | | | |
| Preexperimental | 13 | 4 | 31 | 8 | 62 | 1 | 7 |
| Experimental | 13 | 4 | 31 | 8 | 59 | 1 | 10 |
| Sodium (mg.) | | | | | | | |
| Preexperimental | 105 | 98 | 93 | 2 | 2 | 5 | 5 |
| Experimental | 99 | 91 | 92 | 2 | 2 | 6 | 6 |
| Potassium (mg.) | | | | | | | |
| Preexperimental | 116 | 90 | 78 | 18 | 15 | 8 | 7 |
| Experimental | 131 | 103 | 79 | 18 | 14 | 10 | 7 |
| Cations (mEq.) | | | | | | | |
| Preexperimental | 10.45 | 7.13 | 68 | 2.60 | 25 | 0.72 | 7 |
| Experimental | 10.59 | 7.15 | 68 | 2.55 | 24 | 0.89 | 8 |
| Phosphorus (mg.) | | | | | | | |
| Preexperimental | 53 | 30 | 56 | 18 | 35 | 5 | 9 |
| Experimental | 50 | 28 | 56 | 16 | 32 | 6 | 12 |
| Chlorine (mg.) | | | | | | | |
| Preexperimental | 164 | 151 | 92 | 2 | 1 | 11 | 7 |
| Experimental | 161 | 144 | 90 | 3 | 2 | 14 | 8 |
| Sulfur (mg.) | | | | | | | |
| Preexperimental | 34 | 29 | 88 | 4 | 11 | 1 | 1 |
| Experimental | 32 | 27 | 85 | 4 | 11 | 1 | 4 |
| Anions (mEq.) | | | | | | | |
| Preexperimental | 9.78 | 7.81 | 80 | 1.35 | 14 | 0.62 | 6 |
| Experimental | 9.49 | 7.42 | 78 | 1.24 | 13 | 0.83 | 9 |
| Excess ions ‡ (mEq.) | | | | | | | |
| Preexperimental | 0.67 | 0.68− | .. | 1.25 | .. | 0.10 | .. |
| Experimental | 1.10 | 0.27− | .. | 1.31 | .. | 0.06 | .. |

* The average daily weight gain per kilogram of body weight was: preexperimental period, 0.64 Gm.; experimental period, 0.66 Gm.

† In the absence of methods for the continuous determination of mineral excretion through the skin analytic appraisal cannot be made; therefore, these data include excretion through the skin.

‡ Excess of anions is indicated by a superior minus sign following the figure. If the excess ions are cations, no sign is used.

table 2. By the analysis of variance [18] the differences in values for the preexperimental and experimental periods are statistically significant

17. The basal diet was composed of apple, banana, lean beef, white and whole wheat bread, butter, cabbage, carrots, cheese, eggs, graham crackers, lettuce, milk, peanut butter, potato, shredded wheat or corn flakes, tomato and orange juice, sugar and salt.

18. Snedecor, G. W.: Calculation and Interpretation of Analysis of Variance and Covariance, Ames, Iowa, Collegiate Press, 1934.

for nitrogen, calcium, sodium, potassium, phosphorus, chlorine, sulfur, mineral anions and excess mineral ions in the urine; phosphorus and chlorine in the feces; and nitrogen, sulfur, mineral cations and mineral anions in the retentions. All of the children grew during the study and showed consistent changes in metabolism in response to the inclusion of the larger quantity of banana in the diet, although minor individual variations in response occurred in both the control and the experimental period. Per kilogram of body weight of the 8 children, the rate of gain in weight was 0.64 Gm. per day during the preexperimental period and 0.66 Gm. per day during the experimental period. In no case was there a change in caloric intake greater than 4 calories per kilogram of body weight per day.

The added 100 Gm. of banana daily enhanced the rate of nitrogen storage from 17 to 22 mg. per kilogram of body weight per day, or from 3 to 4 per cent of the intake, although the nitrogen intake was reduced from 506 to 489 mg. per kilogram of body weight. Likewise, the retentions of all the individual acid-base mineral elements were augmented if changed. The facts demonstrate that banana stimulated more rapid growth of both bone and soft tissue, results which corroborate findings of other investigators [19] that physical measurements and rate of skeletal development were increased in children receiving banana and observations in this laboratory that banana increased retention of mineral ions in the children studied.[8]

Banana is an alkalinizing food with a high potassium value, and 100 Gm. of this fruit added to the diet supplied 7.5 milliequivalents (75 cc. of tenth-normal base) of excess mineral cations, resulting in an increase in excess intake of base per kilogram of body weight from 0.67 milliequivalents during the preexperimental period to 1.10 milliequivalents during the experimental period. Although the slightly increased alkaline-ash value of the diet during the experimental period was paralleled by an increased retention of cations, the reduced acid-ash value of the intake was accompanied by a correspondingly increased retention of anions. On a unit weight basis the alkaline-ash and acid-ash values of the intakes during the two periods were 10.45, 10.59 milliequivalents and 9.78, 9.49 milliequivalents respectively, and the apparent retentions 0.72, 0.89 milliequivalents and 0.62, 0.83 milliequivalents respectively, for the preexperimental and experimental observations.

Although the urine is the main pathway of excretion for the metabolized basic and acidic mineral elements, the feces provide a significant outlet for both. The fecal excretion of excess cations was 1.25 milliequivalents (12.5 cc. of tenth-normal base) daily per kilogram of body

19. Roberts, Blair, Austin and Steininger.[1] Roberts, Brooks, Blair, Austin and Noble.[4]

weight during the preexperimental period and 1.31 milliequivalents (13.1 cc. of tenth-normal base) with the additional banana in the diets. During the preexperimental period the urine contained an excess of 0.68 milliequivalents (6.8 cc. of tenth-normal base) of anions per kilogram per day; during the experimental period this figure dropped to 0.27 milliequivalents per kilogram per day, a reduction almost equal to the increase in the alkaline-ash value of the diet with the addition of 100 Gm. of banana.

The greatest difference between the alkaline-ash and acid-ash values of the diets without and with the additional 100 Gm. of banana was in their potassium content, 116 and 131 mg. per kilogram of body weight respectively. The apparent retention of this element increased from 8 to 10 mg. per kilogram per day. Although the daily calcium intake was reduced only by 1 mg. per kilogram of body weight, the apparent retention increased from 4 to 5 mg. per kilogram, or from 11 to 14 per cent of the intake, indicating an enhanced rate of osseous development. The intake and retention of magnesium remained unchanged, and, although the sodium intake was reduced from 105 to 99 mg. per kilogram daily during the experimental period, the apparent daily storage increased from 5 to 6 mg. per kilogram per day.

By increasing the intake of banana the phosphorus intake per day was reduced by 3 mg. (53 to 50) per kilogram of body weight, yet the apparent retention was increased from 5 to 6 mg. (9 to 12 per cent of intake) per kilogram of body weight. Seventy per cent of the phosphorus retained is used in formation of bone, and 30 per cent becomes a component part of the soft tissue. On the other hand, the decreased intake of chlorine was accompanied by a higher retention. Although the daily intake of sulfur was reduced slightly (2 mg. per kilogram), the retention of this element, essential to growth of soft tissue, increased from 1 to 4 per cent of the intake.

This study on the nitrogen and mineral metabolism as influenced by changes in intake of banana has been carried out over a sufficiently long period to offer an opportunity of studying the interaction of the various elements in the formation of bone and soft tissue. It has been shown that supplements of banana increase the total storage of both acidic and basic elements,[2] which demonstrates growth both in bone and in soft tissue. Over 98 per cent of the calcium retained is used in building bone and the ratio of calcium to phosphorus (grams) in bone is 2 : 1. The calcium : phosphorus ratios of intake (0.72) and of retention (0.87) were practically unchanged by the addition of banana to the diet. The calcium : phosphorus retention ratio of less than 1 indicates a rapid synthesis of muscular, neural or glandular tissue, further verified by the nitrogen balances, in which a decreased intake was accompanied by an increased retention (17 to 22 mg. per kilogram of body weight daily).

As nitrogen is utilized it carries with it the major portion of the sulfur, 30 to 40 per cent of the phosphorus retained and some of the potassium. In accordance with the observation of Gordon, Levine, Wheatley and Marples,[20] there was a consistent relation between the percentage of nitrogen retained and the percentages of sulfur, phosphorus and potassium utilized. The increased storage of nitrogen when an additional 100 Gm. of banana per day was fed was paralleled by augmented retentions of sulfur, phosphorus and potassium. An increase in the potassium : sodium ratios with the larger consumption of banana supports the belief that the formation of soft tissue was stimulated to a more rapid rate.

From the facts presented it is evident that banana in the diet has definite nutritive advantage but the modus operandi is still vague. The value of this fruit, however, has been attributed in part to the unique physiologic value of the polysaccharides, namely,[21] pectin and unavailable carbohydrates,[3] in the control of a healthful intestinal medium and elimination, its vitamin content and its alkalinizing effect [22] in the digestive tract.

## SUMMARY

The influence of different levels of banana intake on the nitrogen and mineral balances of 8 normal children, aged 5 to 8 years, was determined during a preexperimental period totaling two hundred and seventy-five days and an experimental period of two hundred and eighty-five days, under controlled conditions which were comparable to the usual home environment. Observations have shown a definite, consistent metabolic response of the subjects to the increased banana intake; therefore, data on the mineral accumulation of the 8 children were averaged for each of the two periods.

On a unit weight basis, ingestion by each child of an additional 100 Gm. of banana daily was accompanied by increased retention or an increased percentage of intake retained of nitrogen, calcium, magnesium, sodium, potassium, phosphorus, chlorine and sulfur. While the retentions of mineral cations and anions both increased during the experimental period, indicating a speeded rate of synthesis of both hard and soft tissue, the storage of excess base per kilogram per day

20. Gordon, H. H.; Levine, S. Z.; Wheatley, M. A., and Marples, E.: Respiratory Metabolism in Infancy and in Childhood: XX. The Nitrogen Metabolism in Premature Infants—Comparative Studies of Human Milk and Cow's Milk, Am. J. Dis. Child. **54**:1030 (Nov.) 1937.

21. Manville, I. A.; Bradway, E. M., and McMinis, A. S.: Pectin as a Detoxication Mechanism, Am. J. Digest. Dis. & Nutrition **3**:570, 1936. Prickett, P. S., and Miller, N. J.: In Vitro Effect of Pectin and Nickel Pectin on Bacterial Growth, J. Pediat. **15**:710, 1939. Hummel, Shepherd and Macy.[3a]

22. Hummel, Shepherd and Macy.[3a] Roberts, Brooks, Blair, Austin and Noble.[4]

was slightly reduced, implying a greater stimulus to construction of soft tissue. This interpretation was supported further by a decreased excess of anions in the urine and by the ratio of calcium : phosphorus retention, which was less than 1 throughout the study. No effect of the additional banana was found in the fecal fat excretion.

From the results of the study the value of including banana in the diets of normal children is clear. The effect of the ascorbic acid or l-malic acid content of the fruit and of the unavailable carbohydrate content, as well as the alkalinizing effect of including larger quantities of banana in the mixed diet, has been discussed in relation to the increased rate of accumulation of nitrogen and mineral elements during the regimen of augmented banana intake.

# INTESTINAL PARASITES IN CHILDREN IN TORONTO

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Few parasitologic surveys have been carried out in Canada. Porter [1] and Fantham and Porter [2] made a survey of human intestinal parasites in Montreal, and Brooks [3] examined stools of 61 persons in Newfoundland. Miller [4] carried out a survey of intestinal parasites of 254 persons in Saskatoon, Saskatchewan, Canada. His survey included 47 children and young adults in an orphan asylum. These surveys were made by examining fecal samples and yielded mainly protozoa. Fantham and Porter, however, in examining the stools of 563 persons, disclosed both protozoa and helminths.

The present report presents the results of a survey of intestinal parasites of children in Toronto, carried out during the winter of 1938 to 1939.

## MATERIAL AND METHODS

The material for this study was obtained mainly from the Hospital for Sick Children and partly from the Thistletown branch of this hospital and the Imperial Order of the Daughters of the Empire Preventorium. The results of a special survey for pinworm infection made by perianal swabbing will be discussed separately from the results of the examinations of stools.

In examining the stool samples the direct smear in saline and iodine solution and the flotation and centrifugation methods were used. Some species of protozoa were cultured. For this purpose the agar slant medium was used, made by the formula previously employed in the School of Hygiene (agar slopes with 7 parts of Locke's solution, without the addition of dextrose, and 1 part of horse serum). Boeck's medium (Locke's solution 4 parts and human serum 1 part) was also

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This survey was carried out with a grant from the Banting Research Foundation, in the Department of Hygiene and Preventive Medicine, under the direction of Dr. Donald T. Fraser, Professor of Hygiene and Preventive Medicine, and in the Department of Paediatrics, University of Toronto, and the Hospital for Sick Children, under the direction of Alan Brown, M.D., F.R.C.P. (Canada), Professor of Paediatrics.

1. Porter, A.: Remarks on Intestinal Parasites in Montreal and the Relation of Entamoeba Histolytica to Colitis, Canad. M. A. J. **33**:134-136, 1934.

2. Fantham, H. B., and Porter, A.: Some Entosoa of Man as Seen in Canada and South Africa, Canad. M. A. J. **34**:414-421, 1936.

3. Brooks, S. T.: A Short Study of Human Parasitism in the Middle North, J. Parasitol. **23**:104, 1937.

4. Miller, M. J.: The Intestinal Protozoa of Man in Midwestern Canada, J. Parasitol. **25**:355-357, 1939.

used for the flagellates, although they were usually cultured in the same medium used for Endamoeba histolytica. Permanent slides, stained with hematoxylin, were made in a few instances only.

A total of 805 fecal samples from 438 children (246 boys and 192 girls) was examined; usually from 1 to 3 samples were obtained from each patient. The total includes 15 samples from nonhospitalized children.

## RESULTS

Of 438 children, 147, or 33.56 per cent, were found to harbor one or more species of protozoa or helminths, as shown in table 1.

Blastocystis hominis, a plant organism belonging to the Blastomycetes, was found in 47 patients. In several instances it was found together with Endamoeba coli, Chilomastix mesnili, Giardia lamblia and Endolimax nana. It occurred in children from 2 to 13 years of age. B. hominis is a common and harmless inhabitant of the human intestine.

TABLE 1.—*Species of Parasites Found in Children in Toronto*

| Species of Parasite | Number of Instances |
|---|---|
| Blastocystis hominis | 47 |
| Chilomastix mesnili | 9 |
| Giardia lamblia | 41 |
| Trichomonas hominis | 3 |
| Endamoeba histolytica | 4 |
| Endamoeba coli | 55 |
| Diendamoeba fragilis | 2 |
| Endolimax nana | 15 |
| Iodamoeba buetschlii | 3 |
| Diphyllobothrium latum | 1 |
| Species of Taenia | 1 |
| Ascaris lumbricoides | 5 |
| Trichocephalus trichiurus | 1 |
| Enterobius vermicularis | 16 |

C. mesnili was found in 9 children, aged 2 to 12. In the cystic stage it was usually found in formed stools, whereas the soft or fluid stools frequently contained more trophozoites than cysts. The cysts of this flagellate readily hatched when the sample was diluted with saline solution and placed in the incubator at 37 C. for from two to three hours. C. mesnili is nonpathogenic.

G. lamblia was found in 41 children, 2 to 13 years of age. Several stool samples, especially those of the younger children, containing G. lamblia were diarrheic. In formed stools this flagellate was found in the cystic stage, while in semifluid and fluid stools both the cysts and the living trophozoites were present. Three of the children (contacts) affected were from outside the hospital. Mild infections with G. lamblia may not give rise to symptoms, but in severe infections the clinical picture may resemble that of amebic dysentery and is described in the literature as giardial or lamblial dysentery.

Trichomonas hominis was found in 2 boys, 3 and 13 years of age, in the medical ward of the Hospital for Sick Children. The third occurrence was in the brother of the older boy. This flagellate was successfully cultured, and it developed well in the medium to which Bacterium alcaligenes was added.

Endamoeba histolytica was found in 3 boys in the medical ward of the Hospital for Sick Children. The fourth occurrence was in a child (contact) outside the hospital. One carrier was 13 years of age; the others were 9 years of age. The first patient was admitted to the hospital on Nov. 21, 1938, the second on December 28 and the third on Jan. 5, 1939. The 13 year old carrier was also infected with E. coli, G. lamblia, Iodamoeba buetschlii, T. hominis, Trichocephalus trichiurus and Endamoeba vermicularis. The examination of his family showed: mother, I. buetschlii; father, E. coli, and brother, E. coli and T. hominis. The second carrier in the hospital was infected with E. histolytica only. Five of his brothers and sisters were examined, 4 of whom carried the following protozoa: J. T., E. histolytica and G. lamblia; G. T., G. lamblia, E. coli and E. nana; D. T., G. lamblia and E. coli, and M. T., G. lamblia. The third carrier of E. histolytica was also infected with E. vermicularis and B. hominis.

The parents of the first boy were born in Czechoslovakia, of the second in Canada and of the third in Poland, but all the children were born in Canada.

Several samples were taken from these 3 patients, and a marked periodicity was noticed in the occurrence of E. histolytica in the stools. For one or a few days there were no cysts in the stools, and then followed a period with numerous cysts. The parasites were usually found in the cystic stage, although in several instances the samples were semifluid and were obtained soon enough to find them in the amebic stage. The cysts from each of the 4 carriers were successfully cultured.

The pathogenicity of E. histolytica is well known. In many persons the infection may persist for years, giving rise to a chronic condition without symptoms or with constipation, attacks of slight diarrhea and pains in the lower part of the abdomen. It has been recorded that extensive ulcerations may exist in the intestine of carriers who have shown no symptoms of diarrhea or dysentery.

E. coli was the most common protozoan parasite found in the children from 3 to 14 years old. This protozoan frequently was found together with G. lamblia, E. nana, C. mesnili or B. hominis. E. coli is a harmless parasite of man.

Diendamoeba fragilis was found in 2 boys, 6 and 12 years of age, in the medical ward of the Hospital for Sick Children. It is probable that the occurrence of this protozoan is more frequent than here recorded,

as the samples obtained from the hospitalized children were usually of formed stools, which were therefore unfavorable for the existence of D. fragilis. In both instances D. fragilis was found in semifluid stools which were passed shortly before the examination of the sample.

Some authors have recorded symptoms of intestinal inflammation due to D. fragilis; others have regarded it as a harmless parasite.

E. nana was disclosed in 15 patients, and in all instances it was found in the cystic stage. It is known as a harmless parasite.

I. buetschlii was found in 2 boys, 12 and 13 years of age, in the Hospital for Sick Children and in 1 boy, 14 years of age, in the Preventorium. The fourth occurrence, not listed, was in the mother of the 13 year old boy. I. buetschlii has never been recorded as pathogenic.

D. latum, the fish tapeworm, was disclosed only once, in a Jewish girl 6 years of age. The child was born in Toronto, and the parents have been in Canada for twenty-five years. The child was treated in the Hospital for Sick Children after the infection was diagnosed in the clinic.

D. latum may not give rise to any symptoms, or it may produce a marked systemic toxemia, the so-called "bothriocephalus anemia." There may be a slight leukocytosis with eosinophilia.

A fragment of a proglottis of a species of Taenia, probably Taenia saginata, was found in the stool sample of a 5 year old boy in the Hospital for Sick Children. No more material was obtained.

Ascaris lumbricoides is the large intestinal round worm. The eggs of this parasite were found in the stools of 4 children. The fifth occurrence was in a child who passed the parasite in the feces during hospitalization. The pathologic changes in ascariasis are divided into two types: (1) those produced by the migrating larvae and (2) those caused by the adult worms. It has been suggested by some authors that children infected with ascaris are physically less developed and mentally less alert than uninfected children. The infection may cause generalized toxemia or nervous symptoms, such as insomnia, twitching and restlessness.

T. trichiurus, the whipworm, was found only once—in a 13 year old boy. The infection apparently was slight, as the number of eggs found in the stool samples was small. Slight infection with Trichocephalus may produce no symptoms, but in severe infection the patients may show nervousness, sympathetic reflexes, insomnia, anorexia and marked eosinophilia. The hemoglobin content may be reduced to 40 or 50 per cent.

E. vermicularis is the human pinworm. The eggs or the entire female parasites were found in 16 stool samples, or in 3.65 per cent of

the children examined. It has long been known that the examination of feces for pinworms is unreliable and that only a small percentage of infections can be detected by this method. The more reliable method of taking perianal swabs was used in obtaining the results given in the second part of this report.

Infection with E. vermicularis may lead to nervousness, insomnia and, occasionally, to anemia. The mucous membrane of the intestine may become seriously inflamed, causing digestive disturbances and nervous symptoms. The migrating female parasites may give rise to pruritus ani, which provokes scratching of the irritated region and results in bleeding, eczema and pyogenic infection of the anal region and perineum. The presence of pinworms in great numbers in the rectum may cause violent rectal colic.

## EXAMINATION FOR E. VERMICULARIS BY PERIANAL SWABBING

Much work on enterobiasis has been done in recent years in the United States, especially in Washington by Dr. E. B. Cram and her co-workers. Incidence of infection in different population groups has been studied, investigative technics have been improved and numerous experiments have been performed with various methods of treatment. In 1937 Dr. M. C. Hall, of the National Institute of Health in Washington, D. C., perfected a new swab which he termed the NIH swab. This swab has been used in the present study and was found reliable in detecting pinworm infection. A detailed description of the swab was given by Hall [5] and by Folan [6] and a list of references on enterobiasis in the United States was supplied by Cram and Reardon.[7]

The NIH swab consists of a cellophane-tipped glass rod, with rounded ends, about 10 cm. long and 4 mm. in diameter, which is pushed through a rubber stopper and fitted into a test tube. A 2.5 mm. square of no. 450 moisture-proof transparent cellophane is held to the rod by a narrow band cut from rubber tubing of about 3 mm. bore.

For the diagnosis of pinworm infection the cellophane-covered tip of the rod is used to swab the perianal regions, preferably in the morning before the patient has had a bath or used the toilet. The cellophane is then removed, mounted in water and examined microscopically for pinworm ova. The rod is sterilized, and its end is tipped with fresh cellophane. By following this procedure each rod can be used repeatedly.

The swabs were taken from the children in six wards of the Hospital for Sick Children, the Thistletown branch and the Preventorium. The swabs in the Hos-

5. Hall, M. C.: Studies on Oxyuriasis: I. Types of Anal Swabs and Scrapers, with a Description of an Improved Type of Swab, Am. J. Trop. Med. **17**:445-454, 1937.

6. Folan, J. P.: The Preparation and Cleaning of the NIH Anal Swab Used in the Diagnosis of Oxyuriasis, Pub. Health Rep. **54**:1392, 1939.

7. Cram, E. B., and Reardon, L.: Studies on Oxyuriasis: XII. Epidemiological Findings in Washington, D. C., Am. J. Hyg. **29**:17-24, 1939.

pital for Sick Children and the Preventorium were taken by me between 7 and 9 in the mornings. The swabs in the Thistletown branch were taken by members of the nursing staff in the mornings, except those from the older boys, 9 to 14 years of age, which were taken by Dr. L. N. Silverthorne in the afternoons. The interval between the swabbings was from two days to one week, and one to six swabs were taken from each child. All patients were of the white race except 2 Negroes and 1 Chinese.

A total of 2,157 swabs were taken of 843 children, 454 boys and 389 girls. The children were from 1 to 16 years of age, as indicated in table 2.

## RESULTS

The tabulated results are:

| | |
|---|---|
| Total number of children examined | 843 |
| Total number infected | 410 |
| Total number noninfected | 433 |
| Percentage infected | 48.63 |

TABLE 2.—*Incidence of Infection with E. Vermicularis in Different Age Groups*

| Age in Years | Number of Children Examined | Number of Children Infected | Per Cent of Children Infected |
|---|---|---|---|
| 1- 2 | 92 | 21 | 23 |
| 3- 5 | 217 | 97 | 45 |
| 6- 8 | 249 | 143 | 57 |
| 9-11 | 166 | 89 | 54 |
| 12-14 | 111 | 56 | 54 |
| 15-16 | 8 | 4 | .. |

TABLE 3.—*Incidence of Pinworm Infection in Three Institutions*

| Hospital | Number of Children Examined | Number of Swabs Taken | Number of Children Infected | Per Cent of Children Infected |
|---|---|---|---|---|
| Thistletown branch | 81 | 224 | 25 | 32.09 |
| I. O. D. E. Preventorium | 67 | 252 | 49 | 73.13 |
| Hospital for Sick Children | 695 | 1,681 | 335 | 48.48 |
| Girls' medical ward | 214 | 626 | 122 | 57.00 |
| Boys' medical ward | 235 | 654 | 125 | 53.20 |
| Infectious ward | 59 | 111 | 23 | 39.00 |
| Boys' surgical ward | 59 | 91 | 24 | 40.70 |
| Girls' surgical ward | 48 | 92 | 27 | 56.20 |
| Babies' surgical ward | 43 | 70 | 5 | 11.60 |
| Clinics | 37 | 37 | 9 | 24.30 |

Table 2 shows that the highest percentage of infection, 57, occurred in the age group from 6 to 8 years and the lowest, 23, in the age group from 1 to 2 years. Since the number examined in the age group from 15 to 16 years is so small, the percentage of infection cannot be considered reliable.

Table 3 shows the number and percentage of children with pinworm infection in the Preventorium, the Thistletown branch and the Hospital for Sick Children.

In the Preventorium the highest percentage of infection, 84.22, was in the age group from 6 to 8 years. The Hospital for Sick Children also showed the highest percentage of infection, 55.5, in the same age group. In the Thistletown branch, however, the highest percentage, 44.44, was in the age group from 12 to 14 years.

The following figures show the manner in which successive swabbings disclosed the presence of the parasites in the 410 infected children:

| | |
|---|---|
| First swab positive | 235 instances, or 57.32% |
| First swab negative, second swab positive | 104 instances, or 25.37% |
| First and second swabs negative, third swab positive | 42 instances, or 10.24% |
| First three swabs negative, fourth swab positive | 29 instances, or 7.07% |
| Five swabs negative | 33 instances |
| Six swabs negative | 4 instances |

Of 410 infected children, 294 were from Toronto and 103 from other parts of Ontario. For 13 patients the place of residence was unknown.

### COMPARISON OF THE RESULTS OF THE SURVEY WITH THOSE OF INVESTIGATIONS IN THE UNITED STATES

There are no data on pinworm surveys for Canada. Investigators in the United States have made extensive surveys in different age and population groups in various parts of the country. Cram and Reardon [7] found that 51 per cent of the children of school age and 35 per cent of those of preschool age were infected with pinworms. These authors and Bozicevich [8] found the incidence of pinworm infection among institutionalized children smaller than among noninstitutionalized. In the present survey the results of examination obtained from the medical wards in the Hospital for Sick Children are probably representative of those from children outside of institutions, as many children in these wards are hospitalized over only a short period. The results of the survey in the Thistletown branch (infection in 32.09 per cent of the children) are almost identical with those given by the previously mentioned authors for institutionalized children. In contrast, the incidence of infection in the Preventorium is much higher than that given in previous records for any institution on this continent.

The value of repeated swabbing has been emphasized by many authors. Cram and Reardon pointed out that the variation in severity of infection influences the frequency of migration of the female parasites to the anal region and their consequent discovery by swabbing. If the infection is slight, there may be certain periods of appearing and of

8. Bozicevich, J.: Studies on Oxyuriasis: III. The Incidence of Pinworm Infestation in a Group of Two Hundred and Thirty Boys in Washington, D. C., M. Ann. District of Columbia **6**:239-241, 1937.

reappearing of the parasites in the anal region. Intervals may also occur between a previous infection and a newly acquired one, that is, when the female parasites of a former infection have deposited all their eggs and the new parasites are developing. The exact duration of the prepatent period of the pinworm is not definitely known, and recent authors generally quote the experiments of Leuckart.[9] In Leuckart's time, however, the modern methods of investigation were unknown, and the diagnosis was based chiefly on fecal examinations.

Cram and Reardon suggested that at least four swabs should be taken, preferably not all on consecutive days, before negative findings can be considered as representing a probable absence of pinworms. The results of the present survey do not permit one to draw a definite conclusion, because the number of swabs taken from each patient varied from one to four. In only a few instances five and six swabs were taken from a child, but these disclosed no additional occurrences of infection.

Had more swabs been taken, the actual incidence of pinworm infection among the children in Toronto would probably have been higher than is indicated by the figures given. It is sufficiently high, however, to show that enterobiasis in Canada is a public health problem of noticeable importance.

SUMMARY

Stool samples of 438 children were examined, and those of 147, or 33.56 per cent, were found to carry one or more species of intestinal protozoa or helminths.

A pinworm survey of 843 children was made in the Hospital for Sick Children, the Thistletown branch of this hospital and the Imperial Order of the Daughters of the Empire Preventorium. The NIH swab (so termed by Hall of the National Institute of Health) was used. The average percentage of infection for all age groups was found to be 48.63. The rate of infection for the Hospital for Sick Children was 48.48 per cent, for the Thistletown branch 32.09 per cent and for the Preventorium 73.13 per cent.

9. Leuckart, R.: Die menschlichen Parasiten und die von ihnen herrührenden Krankheiten, Leipzig, C. F. Winter, 1867, vol. 2, pt. 2, pp. 257-512.

# HOSPITAL MORTALITY AND MORBIDITY OF INFANTILE ECZEMA

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Interest in the allergic aspects of clinical pediatrics has naturally paralleled the greatly increasing general interest that medical men have taken in allergy in recent years. It is evident from the numerous publications regarding allergy in the pediatric journals and from the attendance at pediatric meetings for the discussion of allergy, that the pediatrician is much alive to the necessity for a knowledge of the handling of allergic problems in his practice. Certainly one of the most difficult tasks of the pediatrician is the management of eczematous infants. Some of these patients present extremely complex problems of diet and environment which would seem to be managed best in a hospital. It has, however, long been a popular belief among physicians that the hospital mortality of eczematous infants is unduly high. The pediatric literature in all languages contains numerous reports of hospital deaths, sudden and otherwise, occurring in children with eczema, and warnings against the hospitalization of eczematous infants. It is beyond the scope of this paper to review the literature on this subject, the more important references to which may be found in the communication of Schwartz.[1] It is curious and perhaps significant that no truly scientific studies on the morbidity and mortality of eczematous infants in hospitals were made before that of Koch and Schwartz,[2] who investigated the problem as it occurred in 103 patients with infantile eczema admitted to the Milwaukee Children's Hospital from August 1922 to April 1931. Their conclusions appeared to substantiate the older

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1. Schwartz, A. B.: The Cause of Death in Infantile Eczema, J. Pediat. **4**:172 (Feb.) 1934.

2. Koch, D., and Schwartz, A. B.: The Institutional Mortality and Morbidity of Infantile Eczema, J. Pediat. **2**:169 (Feb.) 1933.

opinions expressed in the literature and already mentioned in this paper. In their series of 56 patients admitted for the treatment of uncomplicated infantile eczema the mortality rate was 17.9 per cent, which, as they pointed out, is higher than the mortality rates reported by Cutler [3] for acute appendicitis (11.4 per cent), empyema (16.4 per cent), pyloric stenosis (11.1 per cent) and fracture of the skull (10.2 per cent).

In studying the publication of Koch and Schwartz,[2] we had the impression that the mortality in our hospital experience was not so high as in theirs. We felt it well, however, to wait until we had a series fairly comparable in number to the series reported by them. In the preparation of this report we have followed the method used by Koch and Schwartz because it permits accurate comparison between our series and theirs and provides a simple model which may be used in the preparation of similar reports from other medical centers. The slight modifications we have made in the method of tabulation add somewhat to the simplicity of the tables and perhaps make them more readable. Thus far we have been unable to discover any similar series of statistical studies. Our series comprises all the eczematous infants up to 2 years of age admitted to the Strong Memorial, the Rochester Municipal and the Genesee Hospital of Rochester from January 1927 through August 1939. In each instance of readmission of an eczematous child, the child was considered as a separate patient. There were 2 patients with two readmissions and 8 patients with one readmission.

Table 1 gives the record of infants who were admitted only for the treatment of eczema and who had no complicating condition at the time of admission. There were 45 such patients. None of these infants died, and all left the hospital improved. In 14 of the infants (31.2 per cent) complications developed, of which otitis media was the most common. In 10 of the infants this disease developed, and in 2 nasopharyngitis occurred. Thus in 12 infants, or 22.6 per cent, of those admitted for treatment of eczema alone, infections of the upper respiratory tract developed. Only 2 infants had other complications (1 erysipelas and 1 furunculosis). Thus 85.8 per cent of the complications originated in the upper respiratory tract. These data are summarized in table 2.

Table 3 is a record of the infants admitted for the treatment of eczema and having an additional diagnosis on admission. No attempt is made to differentiate between infants admitted mainly because of the eczema and those admitted mainly because of the complication. In all patients, however, the eczema was severe enough to warrant its being recorded as the major diagnosis on admission.

3. Cutler, G. D.: Mortality in the Surgical Diseases of Children, Boston M. & S. J. **191**:333 (Aug. 21) 1924.

TABLE 1.—*Data on Infants Admitted for Treatment of Eczema (No Complications at the Time of Admission)*

| Case No. | Month of Admission | Days in Hospital | Age in Months | Complications | Course | Result |
|---|---|---|---|---|---|---|
| 1 | Jan. | 53 | 13 | None | Uneventful | Improvement |
| 2 | Jan. | 18 | 6 | None | Uneventful | Improvement |
| 3 | Jan. | 50 | 11 | None | Uneventful | Improvement |
| 4 | Jan. | 30 | 17 | None | Uneventful | Improvement |
| 5 | Feb. | 30 | 7 | Bilateral acute catarrhal otitis media; bronchitis | Fever; myringotomy | Improvement |
| 6 | Feb. | 22 | 4 | Erysipelas | Stormy | Improvement |
| 7 | Feb. | 11 | 6 | None | Uneventful | Improvement |
| 8 | Feb. | 7 | 8 | None | Uneventful | Improvement |
| 9 | Feb. | 18 | 12 | None | Uneventful | Improvement |
| 10 | Feb. | 19 | 4 | None | Uneventful | Improvement |
| 11 | Feb. | 22 | 7 | Bilateral acute catarrhal otitis media | Myringotomy | Improvement |
| 12 | March | 75 | 12 | None | Uneventful | Improvement |
| 13 | March | 6 | 12 | Nasopharyngitis | Fever | Improvement |
| 14 | March | 11 | 12 | Bilateral acute catarrhal otitis media | Myringotomy | Improvement |
| 15 | March | 19 | 24 | None | Uneventful | Improvement |
| 16 | March | 9 | 11 | None | Uneventful | Improvement |
| 17 | March | 8 | 5 | Acute purulent otitis media | Uneventful | Improvement |
| 18 | April | 5 | 6 | None | Uneventful | Improvement |
| 19 | April | 72 | 7 | Bilateral acute catarrhal otitis media; multiple abscesses; furunculosis | Generalized edema; myringotomy | Improvement |
| 20 | April | 73 | 8 | Bilateral acute catarrhal otitis media | Myringotomy | |
| 21 | April | 76 | 7 | Furunculosis; nasopharyngitis | Uneventful | Improvement |
| 22 | April | 3 | 6 | None | Uneventful | Improvement |
| 23 | April | 10 | 12 | None | Uneventful | Improvement |
| 24 | April | 43 | 11 | None | Uneventful | Improvement |
| 25 | April | 8 | 1 | None | Uneventful | Improvement |
| 26 | April | 8 | 9 | None | Uneventful | Improvement |
| 27 | May | 26 | 2 | None | Uneventful | Improvement |
| 28 | May | 162 | 6 | Bilateral acute catarrhal otitis media; bronchitis | Fever; myringotomy | Improvement |
| 29 | May | 157 | 5 | Bilateral acute catarrhal otitis media; bronchitis | Fever | Improvement |
| 30 | May | 178 | 21 | Furunculosis | Fever | Improvement |
| 31 | May | 54 | 21 | None | Uneventful | Improvement |
| 32 | May | 9 | 22 | None | Uneventful | Improvement |
| 33 | May | 25 | 6 | Bilateral acute catarrhal otitis media | Uneventful | Improvement |
| 34 | June | 47 | 18 | Bilateral acute catarrhal otitis media; nasopharyngitis | Fever | Improvement |
| 35 | June | 40 | 24 | None | Uneventful | Improvement |
| 36 | June | 9 | 12 | None | Uneventful | Improvement |
| 37 | July | 3 | 24 | None | Uneventful | Improvement |
| 38 | Aug. | 8 | 17 | None | Uneventful | Improvement |
| 39 | Aug. | 17 | 24 | None | Uneventful | Improvement |
| 40 | Sept. | 2 | 10 | None | Uneventful | Improvement |
| 41 | Oct. | 10 | 5 | None | Uneventful | Improvement |
| 42 | Oct. | 17 | 19 | None | Uneventful | Improvement |
| 43 | Nov. | 2 | 24 | None | Uneventful | Improvement |
| 44 | Dec. | 9 | 24 | None | Uneventful | Improvement |
| 45 | Dec. | 7 | 14 | None | Uneventful | Improvement |

TABLE 2.—*Summary of Table 1**

| Course During Stay in Hospital | | Number of Patients | Per Cent |
|---|---|---|---|
| Uneventful | | 31 | 68.8 |
| Otitis media | | | |
| (a) Uncomplicated otitis media | 5 | | |
| (b) Otitis media and bronchitis | 3 | | |
| (c) Otitis media and nasopharyngitis | 1 | | |
| (d) Otitis media and furunculosis | 1 | | |
| Total patients with otitis media | | 10 | 22.2 |
| Nasopharyngitis | | 1 | 2.2 |
| Nasopharyngitis and furunculosis | | 1 | 2.2 |
| Erysipelas | | 1 | 2.2 |
| Furunculosis | | 1 | 2.2 |

* There was a total of 45 patients studied. They were admitted to the Strong Memorial Hospital, the Rochester Municipal Hospital and the Genesee Hospital for treatment of eczema only. No deaths occurred, and there was improvement in all cases by the time the patient was discharged from the hospital.

TABLE 3.—*Data on Infants Admitted for Treatment of Eczema with Complications*

| Case No. | Month of Admission | Days in Hospital | Age in Months | Complications | Course | Result |
|---|---|---|---|---|---|---|
| 1 | Jan. | 140 | 5 | Bilateral acute catarrhal otitis media; bronchopneumonia | Myringotomy; convulsions | Improvement |
| 2 | Jan. | 37 | 8 | Erysipelas; bilateral acute catarrhal otitis media | Varicella developed, 3d week | Improvement |
| 3 | Jan. | 23 | 24 | Nasopharyngitis | Fever; uneventful | Improvement |
| 4 | Jan. | 2 | 14 | Asthma | Uneventful | Improvement |
| 5 | Jan. | 7 | 5 | Diarrhea; nasopharyngitis | Uneventful | Improvement |
| 6 | Feb. | 22 | 4 | Erysipelas | Fever; convulsions | Death |
| 7 | Feb. | 60 | 5 | Bilateral acute catarrhal otitis media; impetigo | Fever; myringotomy; transfusions | Improvement |
| 8 | Feb. | 26 | 11 | Bronchitis | Uneventful | Improvement |
| 9 | Feb. | 24 | 6 | Bronchopneumonia | Uneventful | Improvement |
| 10 | March | 7 | 23 | Bilateral acute catarrhal otitis media | Uneventful | Improvement |
| 11 | March | 13 | 12 | Nasopharyngitis | Bilateral acute catarrhal otitis media: myringotomy | Improvement |
| 12 | March | 11 | 19 | Erysipelas | Antiserums; fever | Improvement |
| 13 | March | 22 | 16 | Measles; acute catarrhal otitis media | Pneumonia; myringotomy | Death |
| 14 | March | 10 | 16 | Tetany; acute catarrhal otitis media | Uneventful | Improvement |
| 15 | March | 45 | 16 | Furunculosis | Uneventful | Improvement |
| 16 | April | 3 | 8 | Furunculosis | Fever | Improvement |
| 17 | April | 15 | 13 | Sepsis due to hemolytic streptococci | Transfusions | Improvement |
| 18 | April | 11 | 7 | Erysipelas | Fever; transfusions; antiserums | Improvement |
| 19 | April | 7 | 9 | Acute catarrhal otitis media | Myringotomy | Improvement |
| 20 | April | 7 | 17 | Nasopharyngitis | Uneventful | Improvement |
| 21 | April | 33 | 12 | Bilateral acute catarrhal otitis media | Uneventful | Improvement |
| 22 | April | 11 | 14 | Nasopharyngitis | Uneventful | Improvement |
| 23 | April | 7 | 24 | Nasopharyngitis | Uneventful | Improvement |
| 24 | May | 2 | 8 | Bilateral acute catarrhal otitis media | Myringotomy | Death |

TABLE 3.—*Data on Infants Admitted for Treatment of Eczema with Complications—Continued*

| Case No. | Month of Admission | Days in Hospital | Age in Months | Complications | Course | Result |
|---|---|---|---|---|---|---|
| 25 | May | 87 | 12 | Nasopharyngitis | Acute purulent otitis media; myringotomy | Improvement |
| 26 | May | 26 | 5 | Nasopharyngitis | Uneventful | Improvement |
| 27 | May | 5 | 8 | Asthma | Uneventful | Improvement |
| 28 | May | 14 | 5 | Nasopharyngitis | Uneventful | Improvement |
| 29 | May | 9 | 9 | Bilateral acute catarrhal otitis media | Myringotomy | Improvement |
| 30 | June | 9 | 10 | Nasopharyngitis | Uneventful | Improvement |
| 31 | June | 14 | 10 | Asthma | Uneventful | Improvement |
| 32 | June | 42 | 7 | Nasopharyngitis; asthma; acute purulent otitis media | Myringotomy | Improvement |
| 33 | July | 25 | 10 | Impetigo contagiosa | Fever | Improvement |
| 34 | July | 1 | 8½ | Erysipelas; pneumonia | Death shortly after admission | Death |
| 35 | July | 168 | 4 | Nasopharyngitis; acute catarrhal otitis media | Mastoiditis; due to streptococcic sepsis | Improvement |
| 36 | July | 13 | 9 | Cervical adenitis | Incision and drainage | Improvement |
| 37 | Aug. | 30 | 18 | Diarrhea; cervical adenitis | Incision and drainage of cervical abscess | Improvement |
| 38 | Aug. | 8 | 17 | ?of aspirated foreign body | Bronchoscopy | Improvement |
| 39 | Aug. | 7 | 12 | Nasopharyngitis | Uneventful | Improvement |
| 40 | Sept. | 54 | 24 | Nasopharyngitis | Secondary infection of eczema | Improvement |
| 41 | Sept. | 9 | 18 | Bilateral acute catarrhal otitis media | Uneventful | Improvement |
| 42 | Sept. | 26 | 17 | Nasopharyngitis | Uneventful | Improvement |
| 43 | Oct. | 23 | 6 | Pertussis; asthma | Uneventful | Improvement |
| 44 | Oct. | 12 | 18 | Nasopharyngitis | Uneventful | Improvement |
| 45 | Oct. | 22 | 4 | Harelip; cleft palate | Uneventful | Improvement |
| 46 | Oct. | 24 | 7 | Pertussis | Acute catarrhal otitis media: pneumonia pyelitis | Improvement |
| 47 | Oct. | 14 | 8 | Bilateral acute catarrhal otitis media | Myringotomy | Improvement |
| 48 | Oct. | 15 | 24 | Tonsillitis | Uneventful | Improvement |
| 49 | Oct. | 27 | 36 | Tonsillitis | Uneventful | Improvement |
| 50 | Oct. | 26 | 5 | Cervical adenitis | Incision and drainage | Improvement |
| 51 | Nov. | 38 | 14 | Nasopharyngitis | Uneventful | Improvement |
| 52 | Nov. | 20 | 5 | Scabies | Uneventful | Improvement |
| 53 | Nov. | 5 | 19 | Bilateral acute catarrhal otitis media; urethritis | Uneventful | Improvement |
| 54 | Nov. | 27 | 24 | Acute catarrhal otitis media | Uneventful | Improvement |
| 55 | Nov. | 42 | 14 | Nasopharyngitis | Acute bronchitis | Improvement |
| 56 | Nov. | 18 | 9 | Torticollis | Uneventful | Improvement |
| 57 | Dec. | 200 | 4 | Diarrhea; bilateral acute catarrhal otitis media | Fever; transfusions | Improvement |
| 58 | Dec. | 7 | 4 | Asthmatic bronchitis | Uneventful | Improvement |
| 59 | Dec. | 5 | 6 | Vaccinia | Uneventful | Improvement |
| 60 | Dec. | 37 | 13 | Bronchitis | Pneumonia; acute catarrhal otitis media; myringotomy | Death |
| 61 | Dec. | 30 | 24 | Acute catarrhal otitis media; bronchitis | Myringotomy | Improvement |

There were 61 such patients, among whom 4 deaths occurred, making a mortality of 6.5 per cent. In each fatal case the infant was seriously ill at the time of admission. In 10 infants new complications developed, producing a morbidity of 16.4 per cent. The occurrence of suppuration requiring myringotomy in a patient admitted with a diagnosis of otitis media was not considered as an additional complication.

A summary of the data in table 3 is presented in table 4.

Of the 61 admitted 35 patients, or 57 per cent, had at the time of admission a complication involving the respiratory tract: otitis media, nasopharyngitis, bronchitis or bronchopneumonia.

TABLE 4.—*Summary of Table 3* *

| No. of Cases | Complications at Time of Admission | Uneventful | Complications After Admission | No. | Result |
|---|---|---|---|---|---|
| 15 | Nasopharyngitis | 11 | None | | Improvement |
| | | | Otitis media | 2 | Improvement |
| | | | Secondary infection of eczema | 1 | Improvement |
| | | | Bronchitis | 1 | Improvement |
| 8 | Otitis media | 4 | None | | Improvement |
| | | | Suppuration requiring myringotomy | 4 | Improvement |
| 1 | Otitis media; asthma; nasopharyngitis | | Suppuration requiring myringotomy | 1 | Improvement |
| 1 | Otitis media; bronchitis | | Suppuration requiring myringotomy | 1 | Improvement |
| 1 | Otitis media; bronchopneumonia | | Myringotomy; convulsions | 1 | Improvement |
| 1 | Otitis media; diarrhea | 1 | | | |
| 1 | Otitis media; erysipelas | | Varicella, 3d week in hospital | 1 | Improvement |
| 1 | Otitis media; impetigo | | Suppuration requiring myringotomy | 1 | Improvement |
| 1 | Otitis media; measles | | Suppuration requiring myringotomy; pneumonia | 1 | Death |
| 1 | Otitis media; nasopharyngitis | | Streptococcic septicemia; mastoiditis | 1 | Improvement |
| 1 | Otitis media; tetany | 1 | None | | Improvement |
| 1 | Otitis media; urethritis | 1 | None | | Improvement |
| 3 | Asthma | 3 | None | | Improvement |
| 1 | Asthmatic bronchitis | 1 | None | | Improvement |
| 1 | Asthma and pertussis | 1 | None | | Improvement |
| 1 | Bronchopneumonia | 1 | None | | Improvement |
| 2 | Bronchitis | 1 | None | | Improvement |
| | | | Pneumonia; otitis media | 1 | Death |
| 2 | Cervical adenitis | | Incision and drainage | 2 | Improvement |
| 1 | Cervical adenitis; diarrhea | | Suppurative cervical adenitis | 1 | Improvement |
| 3 | Erysipelas | 2 | None | | Improvement |
| | | | | 1 | Death |
| 1 | Erysipelas; pneumonia | | None | 1 | Death |
| 2 | Furunculosis | 1 | None | | Improvement |
| | | | Pyuria | 1 | Improvement |
| 1 | Harelip; cleft palate | 1 | None | | Improvement |
| 1 | Sepsis due to hemolytic streptococci | 1 | None | | Improvement |
| 1 | Impetigo contagiosa | | Fever | 1 | Improvement |
| 1 | Nasopharyngitis; diarrhea | 1 | None | | Improvement |
| 1 | Pertussis | 1 | Otitis media; pneumonia; pyelitis | | Improvement |
| 1 | Scabies | 1 | None | | Improvement |
| 2 | Tonsillitis | 2 | None | | Improvement |
| 1 | Torticollis | 1 | None | | Improvement |
| 1 | Vaccinia | 1 | None | | Improvement |
| 1 | ?of aspirated foreign body | | Bronchoscopy | 1 | Improvement |

* There were a total of 61 patients studied. They were admitted to the Strong Memorial Hospital, the Rochester Municipal Hospital and the Genesee Hospital for treatment of eczema and additional complications.

Table 5 compares the mortality among the infants in our series (Rochester series) with that among the infants at the Milwaukee Children's Hospital (Milwaukee series). No deaths occurred in the Rochester series among infants admitted for the treatment of eczema alone, while the mortality rate for a similar series in Milwaukee was 17.9 per cent. The mortality for the patients in the Rochester series with complications on admission was 6.5 per cent, as contrasted with

10.6 per cent for the Milwaukee series. The mortality for all patients with infantile eczema in the Rochester series was 3.8 per cent. As previously stated, this rate includes infants up to, but not over, 2 years of age. We have no statistics indicating the general hospital mortality for this age group, but over the period covered by our study the mortality rate for all pediatric patients (exclusive of the newborn, who are treated in the obstetric service) was 7.3 per cent. Thus an eczematous infant entering our hospitals has almost twice the chance of survival as the average pediatric patient. The mortality for the Rochester series of 3.8 per cent of all patients with eczema is about one quarter of that reported for the Milwaukee series, 14.4 per cent, and the morbidity for the Rochester series of 20 per cent is about half that for the Milwaukee series, 43.6 per cent. The differences between the mortality and morbidity rates with regard to eczema for the two series are so great that the last column in table 5, which is the result of the combination of the

TABLE 5.—*Comparative Summary of Records of All Infants Up to 2 Years of Age Admitted for Eczema: Rochester and Milwaukee Series*

| | I Without Complications on Admission | | | II With Complications on Admission | | | I + II Combined Patients | | |
|---|---|---|---|---|---|---|---|---|---|
| | Rochester Series | Milwaukee Series | Totals | Rochester Series | Milwaukee Series | Totals | Rochester Series | Milwaukee Series | Totals |
| Number of cases | 45 | 56 | 101 | 61 | 47 | 108 | 106 | 103 | 209 |
| Number of deaths | 0 | 10 | 10 | 4 | 5 | 9 | 4 | 15 | 19 |
| Mortality, per cent | 0 | 17.9 | 10 | 6.5 | 10.6 | 8.3 | 3.8 | 14.4 | 9.1 |
| Morbidity, per cent | 31 | 58.9 | 47 | 16.4 | 25.5 | 20.3 | 20 | 43.6 | 33 |

two series, has academic interest only. Among 209 eczematous infants 2 years of age or less, studied in the hospital, there were 23 deaths; the mortality rate was thus 9.1 per cent, and the morbidity rate was 33 per cent.

We are unable to offer any satisfactory explanation for the differences between the morbidity and mortality rates of infantile eczema in Milwaukee and in Rochester. One cannot always explain the vagaries of disease, and what may ordinarily be a mild disease in one locality may be a serious disease in another. The two contrasting studies do, however, offer some definite suggestions. The first of these is that a pediatrician practicing in Milwaukee, where eczema in hospitalized infants 2 years of age or less has a mortality of 14.4 per cent, would feel much hesitation about sending an eczematous infant into a hospital for study. The same hesitation would naturally not be felt by a Rochester pediatrician facing a mortality rate of 3.8 per cent. Despite our statistics, however, we feel that the general principle followed by pediatricians applies to eczema as it does to all other diseases of child-

hood; the hospital inpatient department is not the place for an infant who can be adequately treated outside.

The second important suggestion to be drawn from the statistics presented is of the need of similar studies from other medical centers. It would be interesting to obtain a cross section of the morbidity and mortality of infantile eczema throughout this country and indeed wherever similar material exists. What is true for Milwaukee or Rochester may or may not be true elsewhere, but it is certainly important for a pediatrician in any locality to know what he may expect in the way of morbidity and mortality when he sends an eczematous infant to the hospital.

In the report of our series it may be seen that the most common complications of eczema are respiratory infections, especially otitis media, and, as can be seen from the tables, these occur most frequently during the months when infections of the upper respiratory tract are the most prevalent. Koch and Schwartz observed that respiratory infections and diarrhea were the most common complications. These observations bear out the experience of most authors. The complication syndrome of eczema—infection of the upper respiratory tract and diarrhea—must be more than a mere coincidence and is perhaps fundamentally related to the evolution of the allergic person. Speculation along these lines leads to extremely interesting, though of course highly theoretic, considerations.

It is generally accepted that the pathologic condition of the basis of allergic disease consists of two anomalies: (1) edema and (2) spasm of smooth muscle. It is not improbable that there is but a single factor, edema, and that the spasm of smooth muscle is secondary to edema. The major manifestations of allergic disease occur in the respiratory tract, the skin and the gastrointestinal tract. Examination of these three groups of tissues, which at first appear to differ greatly, reveals that they possess at least one common denominator: They are all surface tissues, the tissues which separate the person from his environment. It is brought to the attention of every medical student that the epithelium of the deepest alveolus of the lung or of the most hidden niche of the gastrointestinal tract is a direct continuation of the surface of the body and is in fact a body surface. This circumstance, which is demonstrated to the medical student more to show him an anatomic curiosity than for any other reason, may perhaps have a deeper meaning. The epitheliums of these three groups of tissues are the buffer tissues by means of which the complex human organism contacts, draws nourishment from, and reacts to, the environment. The relation between the epithelium of the skin and that of the respiratory tract is closer than that between these two tissues and the epithelium of the gastrointestinal tract, because both of the former are derived from the ectoderm while the latter is derived

from the endoderm. Perhaps, since all three epithelial groups with their underlying tissues of mesodermal origin have developed in the process of evolution into buffer tissues, they are in a way subject to some of the same peculiarities, and what may cause the allergic reaction of edema in one tissue may have an inherent tendency to cause edema in the others because of a similarity in evolution and function. This primitive relation may also explain why cutaneous tests may elicit positive reactions to antigens affecting the respiratory or the gastrointestinal tract. Further evidence that there may be some truth in this theory is that cutaneous tests give more information regarding disease of the respiratory tract, to which the epithelium of the skin is more closely related from an evolutional standpoint, than they do regarding allergy of the gastrointestinal tract, to which the relation of the epithelium of the skin is more distant.

## SUMMARY AND CONCLUSIONS

Among 106 patients with infantile eczema treated in the pediatric services of the Strong Memorial, the Rochester Municipal and the Genesee Hospital of Rochester, N. Y., there were 4 deaths, making a mortality of 3.8 per cent.

Of the same 106 infants, one or more complications developed in 21, making a morbidity rate of 20 per cent.

Among 45 infants admitted for the treatment of infantile eczema without complications at the time of admission, there were no deaths. In 14, complications developed, making a morbidity of 31 per cent.

The mortality for the entire Rochester series of all eczematous patients up to 2 years of age, 3.8 per cent, was about one quarter that of a similar series in Milwaukee, 14.4 per cent, and about half the mortality for all pediatric patients in the three hospitals over the period in which this study was made, 7.3 per cent. The morbidity for the Rochester series, 20 per cent, was about half that in the Milwaukee series, 43.6 per cent.

It would be desirable to obtain further statistics of a similar nature from other medical centers.

Despite our relatively favorable experience in Rochester, we agree as a matter of pediatric principle with the conclusion of Koch and Schwartz: "Infants having infantile eczema should not be admitted to an infant ward if they can possibly be treated in a home or foster home, supervised by an outpatient department, utilizing the Speedwell technic of Chapin."

The most common complications of eczema are respiratory and gastrointestinal. It is suggested that this is not merely a coincidence, but may perhaps be explained on the basis of evolution and function.

# COW'S MILK TREATED BY BASE EXCHANGE FOR INFANT FEEDING

## METABOLISM OF CALCIUM, PHOSPHORUS AND NITROGEN

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In 1934 three of us [1] undertook a comparative study of the calcium and phosphorus metabolism of a normal infant during the periods he was fed boiled whole cow's milk, milk treated by the base exchange method, and milk acidified with citric acid. The results of this investigation showed that minimum quantities of whole cow's milk treated by the process of base exchange [2] according to the method of Lyman and associates [3] kept a normal growing infant in positive calcium and phosphorus balance. Since treatment of whole milk by the process of base exchange reduces the amount of calcium and phosphorus, the study suggested that the percentage of utilization of these elements was increased.

After our previous report [1] was published, the subject of soft curd milks was critically reviewed by the Council on Foods of the American Medical Association [4] and by Doan.[5] The opinions expressed in both

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1. Hess, J. H.; Poncher, H. G., and Woodward, H.: Factors Influencing the Utilization of Calcium and Phosphorus of Cow's Milk, Am. J. Dis. Child. **48**:1058 (Nov.) 1934.

2. The method consists of a process by which milk previously acidified to about 0.3 per cent with citric acid is passed through an artificial zeolite (sodium aluminum silicate). This results in a readjustment of the salts of the milk, chiefly calcium. The reduction of calcium is from approximately 0.13 to 0.1 per cent, and of phosphorus, from 0.1 to 0.08 per cent. In this manner, ordinary raw cow's milk, which when acted on by rennin produces a large, hard, tough curd can be changed to a milk which produces a soft, fine, flocculent curd.

3. Lyman, J. F.; Browne, E. H., and Otting, H. E.: Readjustment of Salts in Milk by Base Exchange Treatment, Indust. & Engin. Chem. **25**:1297 (Nov.) 1933.

4. The Nutritional Significance of the Curd Tension of Milk, report of the Council on Foods, J. A. M. A. **108**:2040 (June 12); 2122 (June 19) 1937.

5. Doan, F. J.: Soft Curd Milk, J. Dairy Sc. **21**:739 (Nov.) 1938.

reviews was that further evidence was needed to demonstrate that soft curd milks are more readily digested than ordinary pasteurized milk. Concern was also shown for the lowering of the calcium content of milk treated by the process of base exchange. The reviewers stated that the claims of unimpaired nutritive value for base exchange–treated milk were insufficiently substantiated by the data on 1 infant. We thought it desirable, therefore, to repeat our original investigations.

The two most pertinent questions appear to be: First, does the reduction in the calcium and phosphorus content of whole milk by the

TABLE 1.—*Average Intake, Output, Retention and Absorption of Calcium Phosphor*

| | | | | | | Calcium | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Output | | | | | | |
| Milk | Subject | Body Weight in Kg. | Experimental Period in Days | Order of Experimental Periods | Age in Weeks | Intake | Urine | Feces | Total | Retention | Absorption | Per Cent Retention | Per Cent Absorption |
| Boiled whole | F. W. | 7.080 | 12 | 2 | 28 | 118.6 | 3.5 | 92.5 | 96.0 | 22.6 | 26.1 | 19.1 | 22.0 |
| Base exchange-treated | | 6.668 | 12 | 1 | 23 | 88.1 | 2.0 | 66.1 | 68.1 | 20.0 | 22.0 | 22.7 | 25.0 |
| Boiled whole | A. R. | 4.922 | 12 | 2 | 20 | 110.8 | 2.4 | 84.1 | 86.5 | 24.3 | 26.7 | 22.0 | 24.1 |
| Base exchange-treated | | 4.752 | 10 | 1 | 16 | 92.1 | 3.0 | 65.8 | 68.8 | 23.3 | 26.3 | 25.3 | 28.5 |
| Boiled whole | T. L. | 5.855 | 12 | 1 | 25 | 114.9 | 4.0 | 74.3 | 78.3 | 36.6 | 40.6 | 31.8 | 35.4 |
| Base exchange-treated | | 6.607 | 10 | 2 | 29 | 92.9 | 3.6 | 56.7 | 60.3 | 32.6 | 36.2 | 35.1 | 39.0 |
| Boiled whole | M. T. | 5.882 | 12 | 1 | 17 | 112.6 | 3.6 | 74.4 | 78.0 | 34.6 | 38.2 | 30.7 | 34.0 |
| Base exchange-treated | | 6.290 | 12 | 2 | 20 | 89.3 | 1.9 | 64.9 | 66.8 | 22.5 | 24.4 | 25.2 | 27.4 |
| Boiled whole | | 6.826 | 6 | 4 | 23 | 115.4 | 3.1 | 80.7 | 83.8 | 31.6 | 34.7 | 27.4 | 30.1 |
| Base exchange-treated | | 6.594 | 6 | 3 | 21½ | 94.8 | 3.2 | 66.5 | 69.7 | 25.1 | 28.3 | 26.5 | 29.8 |
| Boiled whole | C. K. | 5.638 | 11 | 1 | 19 | 111.0 | 1.1 | 82.9 | 84.0 | 27.0 | 28.1 | 24.3 | 25.3 |
| Base exchange-treated | | 5.885 | 12 | 2 | 23 | 91.3 | 0.7 | 69.2 | 69.9 | 21.4 | 22.1 | 23.4 | 24.2 |
| Boiled whole | | 7.582 | 12 | 4 | 42 | 113.0 | 0.8 | 91.7 | 92.5 | 20.5 | 21.3 | 18.1 | 18.8 |
| Base exchange-treated | | 6.592 | 12 | 3 | 32 | 91.3 | 2.1 | 72.6 | 74.7 | 16.6 | 18.7 | 18.2 | 20.5 |
| Boiled whole | E. P. | 7.405 | 11 | 1 | 23 | 111.4 | 1.1 | 100.1 | 101.2 | 10.2 | 11.3 | 8.6 | 9.5 |
| Base exchange-treated | | 8.618 | 12 | 2 | 29 | 95.3 | 1.1 | 68.2 | 69.3 | 26.2 | 27.6 | 27.7 | 28.9 |
| Boiled whole | | 10.812 | 11 | 5 | 48 | 89.5 | 0.6 | 63.8 | 64.4 | 25.1 | 25.7 | 28.0 | 28.7 |
| Base exchange-treated | | 10.275 | 9 | 3 | 39 | 84.9 | 0.8 | 52.9 | 53.7 | 31.2 | 32.0 | 36.8 | 37.7 |
| Modified with citric acid | | 10.710 | 9 | 4 | 43 | 108.2 | 0.7 | 78.4 | 79.1 | 29.1 | 29.8 | 26.9 | 27.5 |

* Values are expressed in milligrams.
† Protein = nitrogen × 6.37.

process of base exchange have any deleterious effect on the amount of calcium and phosphorus retained [6] and absorbed [7] by normal infants from such feedings? Second, if an adequate amount of these elements and of nitrogen is retained, does this indicate an improved digestibility for this type of milk? The present report is concerned with the presentation of data on these questions.

6. Amount retained = intake minus urinary and fecal excretion; percentage retained = $\frac{\text{amount retained}}{\text{amount ingested}}$.

7. Amount absorbed = intake minus fecal excretion; percentage absorbed = $\frac{\text{amount absorbed}}{\text{amount ingested}}$.

## PLAN OF THE INVESTIGATION

The entire period of observation was fourteen months. The experimental periods were planned to be of twelve days' duration; they were divided into four periods of three days each. The subjects, 6 normal boys under 1 year of age, were under the care of two special nurses who were exclusively assigned to this investigation. During the period of observation the babies were placed on metabolism beds designed for the quantitative collection of urine and stools. The collections were discontinued whenever an elevated temperature, an abnormal physical condition or any other circumstance occurred which might interfere with normal metabolism. This procedure insured that the infants were in good physical condition throughout

*nd Nitrogen per Kilogram of Body Weight per Twenty-Four Hours**

| Phosphorus | | | | | | | | | Nitrogen | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Output | | | | | | | | | Output | | | | | | |
| Intake | Urine | Feces | Total | Retention | Absorption | Per Cent Retention | Per Cent Absorption | Protein† Intake, Gm. | Intake | Urine | Feces | Total | Retention | Absorption | Per Cent Retention | Per Cent Absorption |
| 92.7 | 38.6 | 39.1 | 77.7 | 15.0 | 53.6 | 16.2 | 57.8 | 3.1 | 487.8 | 350.8 | 52.4 | 412.2 | 75.6 | 435.4 | 15.5 | 89.2 |
| 69.5 | 31.0 | 21.7 | 52.7 | 16.8 | 47.4 | 24.2 | 68.2 | 3.0 | 463.9 | 308.6 | 55.2 | 363.8 | 100.1 | 408.7 | 21.6 | 88.1 |
| 83.0 | 48.3 | 18.6 | 66.9 | 16.1 | 64.4 | 19.4 | 77.6 | 3.0 | 481.4 | 333.7 | 57.7 | 391.4 | 90.0 | 423.7 | 18.7 | 88.0 |
| 71.5 | 47.8 | 10.5 | 58.3 | 13.2 | 61.0 | 18.5 | 85.3 | 3.0 | 469.9 | 335.8 | 67.1 | 402.9 | 67.0 | 402.8 | 14.4 | 85.7 |
| 84.9 | 54.6 | 11.8 | 66.4 | 18.5 | 73.1 | 21.8 | 86.1 | 3.0 | 491.4 | 379.7 | 46.1 | 425.8 | 65.6 | 445.3 | 13.4 | 90.6 |
| 71.7 | 46.0 | 7.6 | 53.6 | 18.1 | 64.1 | 25.2 | 89.4 | 3.0 | 468.9 | 366.7 | 40.4 | 407.1 | 61.8 | 428.5 | 13.2 | 91.4 |
| 84.5 | 49.0 | 15.8 | 64.8 | 19.7 | 68.7 | 23.3 | 81.3 | 3.0 | 465.4 | 297.2 | 58.3 | 355.5 | 109.9 | 407.1 | 23.6 | 87.5 |
| 70.1 | 44.1 | 10.8 | 54.9 | 15.2 | 59.3 | 21.7 | 84.6 | 3.0 | 466.4 | 327.8 | 54.8 | 382.6 | 83.8 | 411.6 | 18.0 | 88.3 |
| 87.8 | 50.4 | 17.2 | 67.6 | 20.2 | 70.6 | 23.0 | 80.4 | 2.9 | 458.5 | 323.7 | 49.5 | 373.2 | 85.3 | 409.0 | 18.6 | 89.2 |
| 76.0 | 49.3 | 9.7 | 59.0 | 17.0 | 66.3 | 22.4 | 87.2 | 3.1 | 493.2 | 334.0 | 44.0 | 378.0 | 115.2 | 449.2 | 23.4 | 91.1 |
| 84.0 | 50.9 | 18.6 | 69.5 | 14.5 | 65.5 | 17.3 | 78.0 | 2.9 | 462.9 | 348.1 | 45.3 | 393.4 | 69.5 | 417.6 | 15.0 | 90.2 |
| 71.9 | 48.0 | 11.3 | 59.3 | 12.6 | 60.6 | 17.5 | 84.3 | 3.0 | 475.4 | 370.0 | 40.5 | 410.5 | 64.9 | 434 9 | 13.6 | 91.5 |
| 83.5 | 47.7 | 26.5 | 74.2 | 9.3 | 57.0 | 11.1 | 68.3 | 3.1 | 483.2 | 386.5 | 41.3 | 427.8 | 55.4 | 441.9 | 11.5 | 91.5 |
| 75.3 | 45.2 | 17.3 | 62.5 | 12.8 | 58.0 | 17.0 | 77.0 | 3.1 | 485.6 | 386.3 | 36.8 | 423.1 | 62.5 | 448.8 | 12.9 | 92.4 |
| 85.5 | 38.6 | 35.4 | 74.0 | 11.5 | 50.1 | 13.4 | 58.6 | 3.2 | 501.5 | 354.6 | 80.8 | 435.4 | 66.1 | 420.7 | 13.2 | 83.9 |
| 76.0 | 41.0 | 20.6 | 61.6 | 14.4 | 55.2 | 19.0 | 72.8 | 3.1 | 491.7 | 346.5 | 54.9 | 401.4 | 90.3 | 436.8 | 18.4 | 88.8 |
| 71.4 | 31.6 | 20.0 | 51.6 | 19.8 | 51.4 | 27.8 | 72.0 | 2.6 | 406.8 | 231.4 | 43.5 | 274.9 | 131.9 | 363.3 | 32.4 | 89.3 |
| 66.3 | 32.1 | 15.7 | 47.8 | 18.5 | 50.6 | 27.9 | 76.4 | 2.5 | 392.5 | 265.9 | 36.6 | 302.5 | 90.0 | 355.9 | 22.9 | 90.7 |
| 81.1 | 46.6 | 20.0 | 66.6 | 14.5 | 61.1 | 17.9 | 75.3 | 3.0 | 472.7 | 315.5 | 54.3 | 369.8 | 102.9 | 418.3 | 21.8 | 88.5 |

the intervals of experimental observation. The actual number of days in each experimental period and each infant's age in weeks are indicated in table 1.

All the formulas that were fed to the infants were calculated on the basis of minimum requirements (1½ ounces [45 cc.] of milk and 3 Gm. of lactose per pound of body weight). Minimum standards were adopted since any differences in the two milks would be revealed more readily with minimum than with optimum levels of intake. As the content of fat, carbohydrate and protein of whole cow's milk is not altered by the process of base exchange, an equivalent caloric content was furnished by the two milks fed. The children received daily 6 to 7 cc. of orange juice per kilogram of body weight, 1,700 units of natural vitamin D and 9,400 units of natural vitamin A. The usual additions of cereals, fruits and vegetables were omitted from the diets of the older children, so that conditions would be comparable throughout the experiment.

The whole milk used in the formulas was heated eight minutes in a double boiler; that is, heating was continued for eight minutes after the water in the outer vessel had started to boil. The base exchange-treated milk was fed unboiled. Boiled tap water was used as a diluent in all formulas, since the customary routine feeding procedure was being followed. The children were fed the experimental formulas for at least one week before the specimens for chemical analyses were collected. The intakes were corrected for regurgitations and refusals. During the period of collections an aliquot portion from each daily formula was combined with an aliquot sample of the orange juice for analysis. These aliquots were pooled and samples were taken immediately for an analysis for nitrogen. All the determinations of mineral content were made on ashed samples.

The beginning of each experimental period was marked off with carmine and the end with charcoal. The stools were acidified with glacial acetic acid, digested one-half hour or more on a steam bath, put through a strainer and diluted to a volume of 1,000 or 2,000 cc., as suggested by Stearns.[8] Nitrogen was determined on this fecal emulsion without further treatment. For analyses for mineral content 100 cc. portions were evaporated to dryness on a steam bath and dry ashed.

Seventy-two hour specimens of urine were acidified with hydrochloric acid and preserved in the ice box until the analyses were completed.

## CHEMICAL METHODS

The content of calcium in the formulas and stools was determined by the precipitation method of Washburn and Shear;[9] the amount of oxalate was determined according to the volumetric procedure. The calcium content of the urine was determined by Wang's[10] method. The amount of phosphorus in the urine, formulas and stools was determined by Youngburg's[11] method. The nitrogen content was determined by the standard Kjeldahl procedure, using potassium sulfate, copper sulfate and Hengar selenized granules in the digestion mixture. Triplicate determinations were made on each of the three day specimens.

## RESULTS

The average values of the results of thirty-three periods of feeding of boiled whole milk and thirty-one periods of feeding of unboiled base exchange–treated milk are summarized in table 1 and charts 1, 2 and 3. Statistical analyses[12] of these data are presented in table 2.

*Calcium.*—The 6 subjects studied were all in positive calcium balance when fed minimum amounts of either boiled whole milk (mean

8. Stearns, G.: A Rapid Method for the Preparation of Fecal Digests Suitable for Use in Nitrogen and Mineral Analyses, J. Lab. & Clin. Med. **14**:954 (July) 1929.

9. Washburn, M. L., and Shear, M. J.: Composition of Bone: XIII. Direct Gravimetric Determination of Calcium, Magnesium and Phosphate, J. Biol. Chem. **99**:21 (Dec.) 1932.

10. Wang, C. C.: Improvements in the Methods for Calcium Determination in Biological Material, J. Biol. Chem. **111**:443 (Oct.) 1935.

11. Youngburg, G.: Phosphorus Metabolism: III. On the Determination of Phosphorus in Urine, J. Lab. & Clin. Med. **17**:1145 (Aug.) 1932.

12. Garrett, H. G.: Statistics in Psychology and Education, New York, Longmans, Green & Co., 1939.

retention = 25.5 mg., or 23.1 per cent) or unboiled base exchange–treated milk (mean retention = 23.9 mg., or 26.3 per cent). From table 1 it is apparent that 4 of the 6 infants showed a better percentile

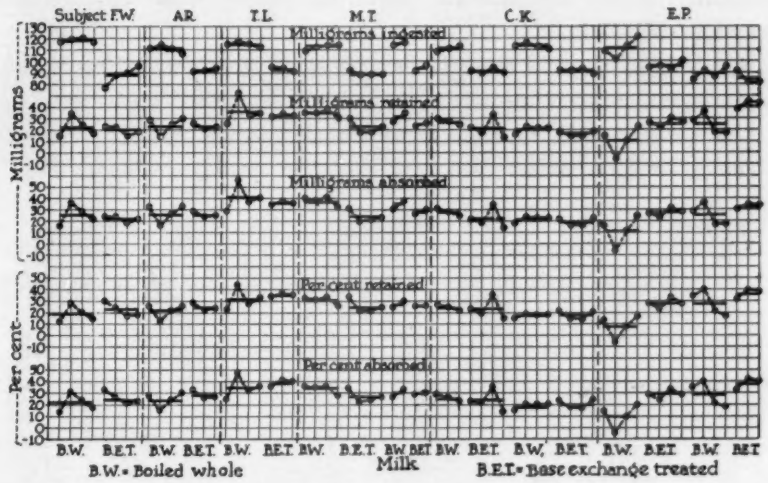


Chart 1.—Ingestion, retention and absorption of calcium from feedings of boiled whole milk and of unboiled base exchange–treated milk. Individual points represent average values per kilogram of body weight per twenty-four hours. The heavy line indicates the mean for the experimental period.

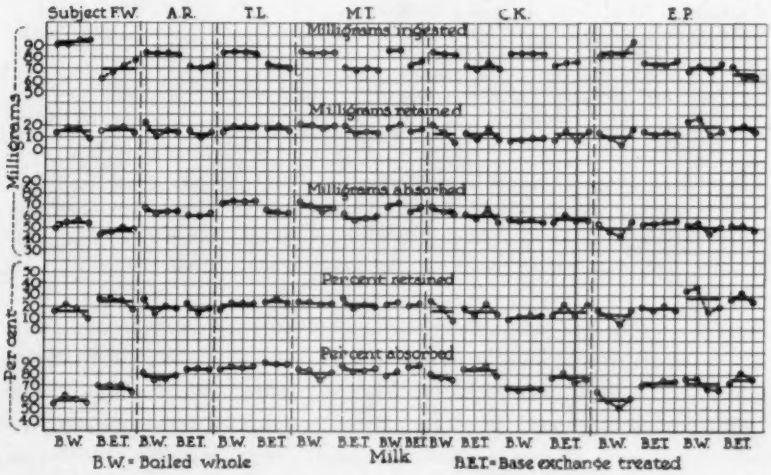


Chart 2.—Ingestion, retention and absorption of phosphorus from feedings of boiled whole milk and of unboiled base exchange–treated milk. Individual points represent average values per kilogram of body weight per twenty-four hours. The heavy line indicates the mean for the experimental period.

retention and absorption of unboiled base exchange–treated milk. The third subject, M. T., showed a somewhat better percentile and absolute retention of boiled whole milk, whereas the sixth subject, E. P., showed a definitely better absolute and percentile retention of unboiled base exchange–treated milk.

*Phosphorus.*—All of the infants were in positive phosphorus balance on minimum intakes of either boiled whole milk (mean retention = 15.9 mg., or 19.1 per cent) or unboiled base exchange–treated milk (mean retention = 15.2 mg., or 21.2 per cent). The 6 subjects

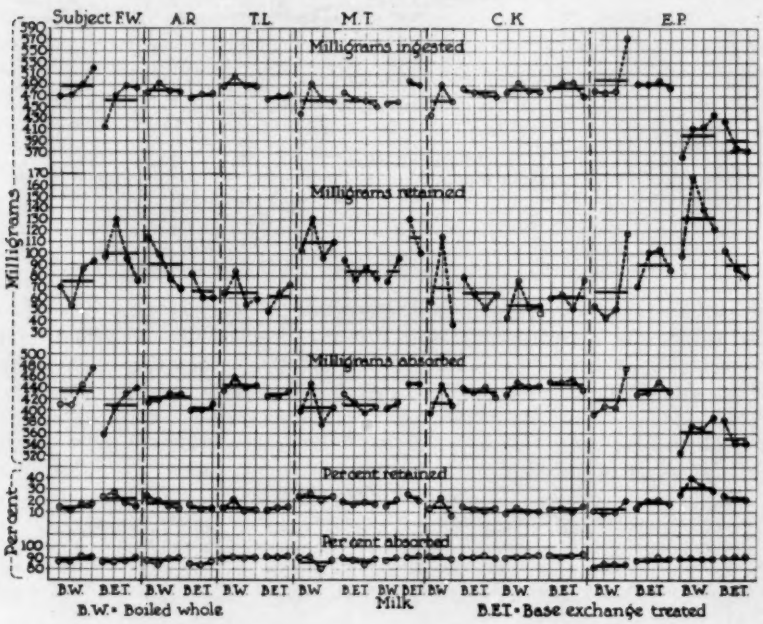


Chart 3.—Ingestion, retention and absorption of nitrogen from feedings of boiled whole milk and of unboiled base exchange–treated milk. Individual points represent average values per kilogram of body weight per twenty-four hours. The heavy line indicates the mean for the experimental period.

absorbed a higher percentage of the phosphorus ingested from unboiled base exchange–treated milk (mean value = 79.7 per cent) than from boiled whole milk (mean value = 72.7 per cent); the absolute amounts of phosphorus absorbed, however, were essentially the same from the two milks (mean values = 60.9 mg. from boiled whole milk and 57.5 mg. from unboiled base exchange–treated milk).

*Nitrogen.*—The protein supplied by 1½ ounces (45 cc.) of milk per pound (453 Gm.) of body weight kept all of the infants in positive nitrogen balance. The mean values presented in table 2 show that the absolute amounts and the percentages of nitrogen retained and absorbed were

similar for feedings of formulas prepared from boiled whole milk and from unboiled base exchange–treated milk. Irrespective of the type of milk fed, approximately 400 mg. of nitrogen per kilogram per twenty-four hours was absorbed.

TABLE 2.—*Statistical Analysis of Ingestion, Retention and Absorption of Calcium, Phosphorus and Nitrogen*

| Milk | | Mean | Standard Error of the Mean | Standard Deviation | Standard Error of Standard Deviation | D/S.E.D* | Odds† |
|---|---|---|---|---|---|---|---|
| | | **Calcium** | | | | | |
| ‡Boiled whole | Mg. ingested | 110.5 | 1.5 | 8.8 | 1.1 | 11.2 | |
| §Base exchange-treated | | 91.2 | 0.78 | 4.4 | 0.56 | | |
| Boiled whole | Mg. retained | 25.5 | 1.8 | 10.4 | 1.3 | 0.76 | 3 to 1 |
| Base exchange-treated | | 23.9 | 1.1 | 6.1 | 0.78 | | |
| Boiled whole | Mg. absorbed | 27.7 | 1.9 | 11.0 | 1.4 | 0.74 | 3 to 1 |
| Base exchange-treated | | 25.8 | 1.7 | 9.6 | 1.2 | | |
| Boiled whole | Per cent retained | 23.1 | 1.7 | 9.5 | 1.2 | 1.54 | 1 to 13 |
| Base exchange-treated | | 26.3 | 1.2 | 7.0 | 0.89 | | |
| Boiled whole | Per cent absorbed | 25.4 | 1.6 | 9.1 | 1.1 | 1.48 | 1 to 13 |
| Base exchange-treated | | 28.4 | 1.3 | 7.0 | 0.89 | | |
| | | **Phosphorus** | | | | | |
| Boiled whole | Mg. ingested | 83.9 | 1.0 | 6.0 | 0.74 | 9.3 | |
| Base exchange-treated | | 72.0 | 0.75 | 4.2 | 0.53 | | |
| Boiled whole | Mg. retained | 15.9 | 0.95 | 5.4 | 0.66 | 0.62 | 3 to 1 |
| Base exchange-treated | | 15.2 | 0.59 | 3.3 | 0.42 | | |
| Boiled whole | Mg. absorbed | 60.9 | 1.5 | 8.7 | 1.1 | 1.82 | 24 to 1 |
| Base exchange-treated | | 57.5 | 1.1 | 6.0 | 0.76 | | |
| Boiled whole | Per cent retained | 19.1 | 1.2 | 7.1 | 0.87 | 1.4 | 1 to 11 |
| Base exchange-treated | | 21.2 | 0.8 | 5.0 | 0.64 | | |
| Boiled whole | Per cent absorbed | 72.7 | 1.8 | 10.1 | 1.2 | 3.18 | 1 to 1,000 |
| Base exchange-treated | | 79.7 | 1.3 | 7.4 | 0.94 | | |
| | | **Nitrogen** | | | | | |
| Boiled whole | Mg. ingested | 472.0 | 6.0 | 34.6 | 4.3 | 0.47 | |
| Base exchange-treated | | 468.2 | 5.4 | 30.2 | 3.8 | | |
| Boiled whole | Mg. retained | 83.6 | 5.5 | 31.4 | 3.9 | 0.48 | 2 to 1 |
| Base exchange-treated | | 80.4 | 3.7 | 20.4 | 2.6 | | |
| Boiled whole | Mg. absorbed | 418.8 | 5.4 | 31.8 | 3.9 | 0.17 | 1 to 1 |
| Base exchange-treated | | 420.1 | 5.3 | 29.6 | 3.8 | | |
| Boiled whole | Per cent retained | 18.1 | 1.3 | 7.5 | 0.92 | 0.52 | 2 to 1 |
| Base exchange-treated | | 17.3 | 0.83 | 4.6 | 0.58 | | |
| Boiled whole | Per cent absorbed | 88.8 | 0.49 | 2.8 | 0.34 | 0.43 | 1 to 2 |
| Base exchange-treated | | 89.7 | 0.44 | 2.5 | 0.31 | | |

* The difference between the two means divided by the standard error of that difference.
† Calculated from table 34 of Garrett,[12] p. 213, giving the chances in 100 for a given value of D/S.E.D.
‡ Fed for 33 experimental periods.
§ Fed for 31 experimental periods.

*Curd Tension.*—Determinations of curd tension were made on the milks used in this investigation with the exception of milk acidified with citric acid, which was already in a finely divided curded state. The tentative method of the American Dairy Science Association[13] and the American curd-o-meter instrument with a hydraulic lift were used. The curd tension of boiled whole milk ranged from 7 to 12 Gm., and

13. Report of the Curd Tension Committee, read before the Annual Meeting of the American Dairy Science Association, Columbus, Ohio, June 1938.

that of unboiled base exchange–treated milk from zero to 10 Gm., three high values being omitted. We observed, as have others,[14] that occasionally base exchange–treated milk had a curd tension between 20 and 30 Gm. A closer study of these samples revealed that the $p_H$ of the whey was lower than that specified by the American Dairy Science Association's tentative method. The decreased buffer value of the milk apparently caused the formation of a mixture of an acid and a pepsin curd, rather than a true pepsin curd. If the amount of acid used in determining the curd tension was decreased sufficiently to give a whey with a $p_H$ between 5.95 and 6.1, the values for curd tension of the milk dropped to within the average range for unboiled base exchange–treated milk.

Miller,[15] using the hydrochloric acid pepsin coagulant, studied raw, boiled and homogenized milks. He stated that the values for curd tension were practically alike when hydrochloric acid concentrations varied from 0.2 to 0.5 per cent. Evidently these variations in the concentration of hydrochloric acid exerted only slight changes on these milks. He selected a concentration of 0.4 per cent acid because it approximates the optimum hydrogen ion concentration of the pepsin. Apparently curd tension is sensitive to changes in concentration of acid and pepsin. The $p_H$ of the whey should be kept within the limits set by the tentative method of the American Dairy Science Association ($p_H$ 5.95 to 6.10) in order to obtain accurate determinations of curd tension.

## COMMENT

*Curd Tension.*—Since the work of Hill[16] in 1931, the attention of the medical profession has been called repeatedly to the various types of soft curd milks. The differences between naturally occurring soft curd and hard curd milks have been studied by Weisberg and associates[17] and by Doan and Welch.[18]

The original method of Hill,[19] using calcium chloride and pepsin as a coagulant for determining curd tension, has been modified, and

14. Doan, F. J., and Flora, C. C.: Comparative Digestibility of Some Soft Curd Milks in Vitro, Bulletin 380, Pennsylvania Agricultural Experiment Station, April 1939.

15. Miller, D.: The Determination of Curd Tension by Use of Hydrochloric Acid-Pepsin Coagulant, J. Dairy Sc. **18**:259, 1935.

16. Hill, R. L.: Soft-Curd Milk, Bulletin 227, Utah Agricultural Experiment Station, June 1931.

17. Weisberg, S. M.; Johnson, A. H., and McCollum, E. V.: Laboratory Studies on the Chemistry of Soft Curd Milks, J. Dairy Sc. **16**:225, 1933.

18. Doan, F. J., and Welch, R. C.: Soft-Curd Milk, Bulletin 312, Pennsylvania Agricultural Experiment Station, December 1934.

19. Hill, R. L.: A Test for Determining the Character of the Curds from Cow's Milk and Its Application to the Study of Curd Variance as an Index to the Food Value of Milk for Infants, J. Dairy Sc. **6**:509, 1923.

a tentative method using hydrochloric acid and pepsin as a coagulant has been adopted by the American Dairy Science Association. According to the arbitrary standards selected by Hill, any milk having a curd tension below 30 Gm. is considered a soft curd milk. Hill expressed the belief that determination of the curd tension by the method he had devised gave a reliable index of the digestibility of milk. Experience with this method over a period of years has led to increasing doubt of the reliability of the curd tension test as a measure of digestibility, especially when applied to the modified fluid milks.

Doan and Flora [14] expressed the opinion that the size of the curd particle is a more accurate index of the suitability of a milk for infant feeding than is curd tension. While this is generally true, porosity of the curd structure should not be overlooked. Espe and Dye [20] pointed out that any factor which tends to make the digesting mass in the stomach more porous increases its ability to absorb gastric juice readily and thus shortens the digestive period.

*Calcium and Phosphorus Metabolism.*—The infant reported on in 1934 [1] and the 6 additional infants studied in the present investigation were all in positive calcium and phosphorus balance on minimum feedings of unboiled milk treated by the process of base exchange (1½ ounces [45 cc.] of milk per pound [453 Gm.] of body weight).

Mitchell, Outhouse and co-workers [21] in a recent study of preschool children have shown that only a small proportion of the calcium ingested is utilized by the growing child. They determined the minimum intake of calcium which would produce maximum retention. Increasing the intake above this amount did not significantly increase retention. They found that when submaximal levels of calcium were fed the percentage of retention correctly gaged the child's ability to utilize calcium.

The results obtained from our investigation of the calcium metabolism of the babies corroborates the belief of Mitchell, Outhouse and associates [21] concerning the influence of the amount of calcium ingested on the retention of this mineral.

Although the inherent calcium content of whole boiled milk is greater (mean value = 110.5 mg.) than that furnished by unboiled base exchange–treated milk (mean value = 91.2 mg.), a statistical analysis

20. Espe, D. L., and Dye, J. A.: Effect of Curd Tension on the Digestibility of Milk, Am. J. Dis. Child. **43**:621 (Jan.) 1932.

21. (*a*) Outhouse, J.; Kinsman, G.; Sheldon, D.; Twomey, I.; Smith, J., and Mitchell, H. H.: The Calcium Requirements of Five Pre-School Girls, J. Nutrition **17**:199 (March) 1939. (*b*) Kinsman, G.; Sheldon, D.; Jensen, E.; Bernds, M.; Outhouse, J., and Mitchell, H. H.: The Utilization of the Calcium of Milk by Pre-School Children, ibid. **17**:429 (May) 1939.

of the data showed that the absolute amounts of calcium absorbed and retained from the two milks were similar.

Examination of the data on phosphorus metabolism presented in tables 1 and 2 revealed that, notwithstanding the greater phosphorus content of the formulas prepared from boiled whole milk (mean value = 83.9 mg.), the values for absolute retention and absorption were not decreased when the infants were fed unboiled base exchange–treated milk (mean intake = 72 mg.). Throughout the entire study a higher proportion of phosphorus was absorbed whenever the infants were receiving unboiled base exchange–treated milk. That these positive results were not due to chance has been confirmed by the statistical interpretation, which showed a significant ratio of 1,000 to 1 in favor of a greater percentage of absorption (7.1 per cent) of the phosphorus in unboiled base exchange–treated milk.

We realize that the purpose of boiling milk for use in infant formulas is to produce a lower curd tension and also a finer curd than is found in the same milk in the pasteurized or raw state. The purpose of the treatment of milk by base exchange is to improve the digestibility of the nutrients by modifying the curd, so that it can be fed unboiled to the infant.

Rogers and associates [22] found that unboiled base exchange–treated milk was superior both to ordinary cow's milk and to acidified milk for complemental feedings of the newborn infant. They also reported that base exchange–treated milk was more suitable for a routine formula. Constipation and regurgitation were materially lessened. Doan and Flora [14] studied the comparative digestibility of soft curd milks in vitro. These authors noted that base exchange–treated milk was digested more readily after than before treatment by base exchange. Reynolds and Macy [23] observed that base exchange–treated milk left the stomachs of children more rapidly than untreated pasteurized cow's milk and slightly faster than evaporated milk.

The following results of our investigation indicated that unboiled base exchange–treated milk was more digestible than boiled whole cow's milk: In general, the infants while being fed unboiled base exchange–treated milk had stools that were better formed and more homogeneous than when boiled whole milk was fed. Although the absolute amounts of phosphorus absorbed from the two milks were similar, the

22. Rogers, A.; Pavey, C. W., and Williams, A.: Complemental Feeding of the Newborn: A Comparison of Plain Cow's Milk with Cow's Milk Modified by the Base Exchange Method, Ohio State M. J. **30**:441 (July) 1934.

23. Reynolds, L.; Macy, I. G., and Souders, H. J.: Gastro-Intestinal Response of Children to Test Meals of Barium and Pasteurized, Evaporated and Base Exchanged Milks, J. Pediat. **15**:1 (July) 1939.

percentage of phosphorus absorbed was unquestionably augmented whenever unboiled base exchange–treated milk was fed. When the intake of an element is lowered, a greater proportion of the amount present must be digested in order to give the same absolute values for absorption. The decrease in phosphorus intake when base exchange–treated milk was fed was compensated for by a decrease in fecal excretion. This was also true for calcium. The increment in the per cent of phosphorus absorbed may be interpreted as due to an increased absorbability of the phosphorus in base exchange–treated milk, since the amount of phosphorus absorbed represents the quantity ingested minus that eliminated through the intestinal tract. Apparently, if the elements are rendered available, the body will take as much as it requires and excrete that which it does not need. There was no evidence, therefore, of impaired nutritive value brought about by the reduction of calcium and phosphorus through the treatment of milk by base exchange.

The improved digestibility of a milk has often been interpreted as indicating improved utilization of its elements. Doan and Flora [14] observed excellent digestibility of acidified milks in vitro. Our data on phosphorus confirmed this contention as far as digestibility of citric acid milk was concerned. However, when milk acidified by citric acid was fed, a larger amount of phosphorus was excreted in the urine and decreased retention resulted. This was shown by the data on E. P. in this study and in the work reported in 1934.[1] Accordingly, it would appear that the increased digestibility of a milk is not necessarily paralleled by an increased retention of its elements.

In the comparison in 1934 [1] of the results obtained from acidified milk with those from the base exchange–treated milk, we suggested that some factor other than size of the curd and amount of soluble calcium might be responsible for the higher percentage retention of calcium and phosphorus from base exchange–treated milk. Determinations of the total base were done for 1 subject, E. P. The total base of the milks varied widely, and no correlation could be found between the total base of the milk and the calcium retention. These determinations do not, however, eliminate the possible influence of one or more of the component bases (magnesium, sodium and potassium).

A growing volume of evidence has been appearing in the literature, indicating that a favorable influence is exerted on calcium metabolism by citrates. Shohl [24] found that the addition of citric acid–sodium citrate mixtures to rachitogenic diets altered them so that they no longer produced rickets. Both the acid reaction and the alkaline ash

24. Shohl, A. T.: The Effect of the Acid-Base Content of the Diet upon the Production and Cure of Rickets with Special Reference to Citrates, J. Nutrition **14**:69 (July) 1937.

factor were necessary to accomplish this result. He also showed that this antirachitogenic factor is the property of citrates and tartrates alone and that the reaction cannot therefore depend entirely on the acid-base effects of the salt. Hamilton and Dewar [25] reported that sodium citrate and sodium tartrate and citric acid and tartaric acids were effective in preventing and curing rickets. Hathaway and Meyer [26] found that the addition of citrates increased the values of bone ash of rats fed rachitogenic diets. They observed that the citrate salts were approximately as effective as the acid-salt mixture.

The presence of an increased amount of citrate in base exchange–treated milk, due to the acidulation of the milk with citric acid prior to the treatment by base exchange, may be a factor which favorably influences the metabolism of calcium and phosphorus.

*Nitrogen.*—A minimum intake of 1½ ounces (45 cc.) of milk per pound (453 Gm.) of body weight furnished 3 Gm. (± 0.1 Gm.) of protein per kilogram per twenty-four hours. Cowie [27] stated that 2.5 to 3.5 Gm. of protein per kilogram should be fed to infants aged from 2 to 12 months. According to the work of Holt and Fales,[28] artificially fed infants should be given up to the age of 9 months from 3 to 4 Gm. of protein per kilogram of body weight. Zahorsky [29] recently reported that artificially fed infants grew better when fed from 3.5 to 4 Gm. of protein per kilogram of body weight.

A selection of the lower limits of the protein requirements suggested for artificially fed infants provided a method of ascertaining whether, in comparison to boiled whole milk, feedings of unboiled base exchange–treated milk would supply the babies with sufficient protein to keep them in positive nitrogen balance and allow for maintenance and growth.

In contrast to the intakes of calcium and phosphorus, the statistical analysis of our results (table 2) showed that despite the fluctuations seen in table 1, there was no significant difference between the amount of nitrogen ingested from boiled whole milk (mean value = 472 mg.) and that from unboiled base exchange–treated milk (mean value = 468.2 mg.).

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25. Hamilton, B., and Dewar, M. M.: Effect of Citrate and Tartrate on Experimental Rickets, Am. J. Dis. Child. **54**:548 (Sept.) 1937.

26. Hathaway, M. L., and Meyer, F. L.: Citric Acid and Its Salts as Calcifying Agents in Rats, J. Nutrition **17**:419 (May) 1939.

27. Cowie, D. M.: A Graphic Chart Method of Studying and Teaching the Principles of Infant Feeding, Am. J. Dis. Child. **4**:361 (Dec.) 1912.

28. Holt, L. E., and Fales, H. L.: The Food Requirements of Children: II. Protein Requirement, Am. J. Dis. Child. **22**:371 (Oct.) 1921.

29. Zahorsky, J.: The Protein Requirements of Infants, Arch. Pediat. **56**: 311 (May) 1939.

From the data presented in table 1, it is to be noted that 5 of the 6 children who were observed did tolerate boiled whole milk as well as unboiled base exchange–treated milk. No superiority in the absorbability of the nitrogen present in milk subjected to the process of base exchange was demonstrated. In contrast to these 5 infants, E. P., at the beginning of the experiment, displayed an intolerance of boiled whole milk; this was shown by his high fecal loss and lowered percentage absorption of nitrogen. After an interval of twenty-five weeks following the first study with boiled whole milk, E. P.'s second period of feedings with boiled whole milk showed a percentage of milk digested equivalent to that displayed on feedings of unboiled base exchange–treated milk. This marked improvement may be explained by changes that occurred with age in E. P.'s physiologic condition which augmented his capacity to digest boiled whole milk.

The statistical interpretation of the results further showed that for the 6 infants studied there were no significant differences in the absolute amounts or percentages of nitrogen retained and absorbed with feedings of either boiled whole milk or unboiled base exchange–treated milk. Since the nitrogen present was, in general, absorbed with equal facility from the two milks, it appears that the protein in boiled whole milk and that present in unboiled base exchange–treated milk furnished equivalent amounts of available nitrogen.

## SUMMARY AND CONCLUSIONS

1. Unboiled base exchange–treated milk, when fed in the proportion of 1½ ounces (45 cc.) per pound (453 Gm.) of body weight, kept 6 infants below the age of 1 year in positive calcium, phosphorus and nitrogen balance.

2. Essentially the same absolute amounts of calcium, phosphorus and nitrogen were absorbed and retained from the boiled whole milk as from the unboiled base exchange–treated milk.

3. The percentage of phosphorus absorbed was definitely higher from unboiled base exchange–treated milk than from boiled whole milk

4. There was no difference in the availability of nitrogen from these two milks.

5. The reduction of the calcium and phosphorus content of milk by the process of base exchange does not impair the nutritive value of this milk.

# ABSORPTION OF POLIOMYELITIS VIRUS BY POSSIBLY DEFICIENTLY MEDULLATED NERVES

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The dictum has been formulated that poliomyelitis virus has an almost obligate affinity for gray nerve fibers.[1] When the virus is injected into medullated peripheral nerves of a normal Macaca mulatta monkey its spread is resisted, unless there has been previous manipulation whereby gray-fibered axis-cylinders have become exposed.[2] Even under these conditions, the disease is difficult to produce. It may be concluded, therefore, that poliomyelitis virus has but a slight affinity for the exposed axons of peripheral medullated nerves, and, by inference, it might be deduced that its spread to the central nervous system is stopped by the myelin contained in the sheath which covers the gray fibers. This would explain why there is not in every case of poliomyelitis involvement of the vagus nerve, which is actually a bundle of well medullated connector fibers, the postganglionic unmedullated gray fibers of which are found in the walls of the intestines. Although the latter gray fibers might be partly or completely involved in every case of poliomyelitis, few symptoms of this involvement other than constipation would become manifest clinically. These dictums suggest reasons why the virus can travel unimpeded along the gray fibers of the gastrointestinal postganglionic sympathetic nerve fibers and up and down the pathways of the sympathetic nervous system to the cerebral and lumbar segments of the spinal cord, where there are gray but no white rami communicantes.

It should be possible to determine whether these principles hold true in another part of the body, that is, in the adrenal gland. The medullary innervation of this gland, like that of the intestine and other hollow

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1. Toomey, J. A.: An Explanation of the Mechanism of Infantile Paralysis Production in the Human Being, Ann. Int. Med. 8:854, 1935.

2. Toomey, J. A.: Adsorption of Poliomyelitis Virus by Various Materials, in Report of Proceedings, Third International Congress of Microbiology, New York, The Congress, 1940, p. 328.

organs, might be considered postganglionic in type.[3] The immediate postganglionic nerve fibers are limited to the organ itself and are thus unmedullated, while nearly all the secondary preganglionic fibers are medullated as far as the cortex of the gland. The myelinated cover constitutes a good insulating sheath for the nerve.

The adrenal receives its nerve supply from the adrenal plexus, most of the fibers of which are myelinated and arise from the celiac plexus. These fibers are connected with the phrenic plexus above and the renal plexus below. Thus, fibers run from the greater splanchnic, vagus and phrenic nerves directly to the gland.

Two general groups of nerve fibers to the adrenal are postulated. 1. There are those from the great splanchnic nerve, which are derived in part directly and in part indirectly from a large adrenal ganglion, the fibers of which are actually connector fibers ending about the excitor and chromaffin cells. 2. There are those derived from the celiac plexus, which are largely destined for the cortex. In the medulla of the adrenal nonmedullated nerve fibers of the autonomic nervous system terminate, possibly in synaptic contact with either the chromaffin or the ganglion cells. The fibers to these cells might be considered preganglionic in type and the chromaffin cells homologous with peripheral neurons of the autonomic system and, for practical purposes, postganglionic in character. Most fibers lose their myelin sheath as they enter the gland, so that relatively few myelinated fibers are found in the medulla, most of them being in the capsule, in the superficial portions of the gland and in the cells of the cortex.

Virus injected into the adrenals of normal monkeys might attack the peripheral, postganglionic, unmedullated neurons in the medulla of the gland, but the spread of the virus to the central nervous system should be stopped by the preganglionic medullated fibers which run directly to the capsule of the organ.

### EXPERIMENT 1

Abdominal sections were performed on 8 Macaca mulatta monkeys weighing from 1,600 to 1,800 Gm., complete ether anesthesia being used. The viscera were exposed, and a dose of a suspension of poliomyelitis virus (from 2 per cent to 10 per cent) was injected into the center of the left adrenal. Six tenths of a cubic centimeter was the maximum amount that could be injected without rupturing the gland. Pressure was applied both to the adrenal vessels and at the site where the needle entered, so that approximation of virus and cells could occur. Furring was seen in all of the animals for a few days after the operation, but no paralysis occurred. One animal given an injection on Dec. 19, 1934 of 0.6 cc. of a 2 per cent

3. (*a*) Cunningham, D. J.: Manual of Practical Anatomy, ed. 6, New York, Oxford University Press, 1931, p. 1320. (*b*) Kuntz, A.: The Autonomic Nervous System, Philadelphia, Lea & Febiger, 1929, p. 268. (*c*) Wright, S.: Applied Physiology, ed. 3, New York, Oxford University Press, 1929, p. 131.

virus suspension, gradually wasted away and died on Jan. 27, 1935, thirty-nine days later. At autopsy the left adrenal was moderately enlarged, with a peripheral zone of redness and a gray center. Other organs were normal. Microscopic examination of the lumbar, cervical and bulbar areas of the central nervous system showed a decrease in the number of anterior horn cells, while those that remained were shrunken. There was an increase in the number of neuroglia cells, but there was no infiltration of lymphocytic cells, no cuffing and no capillary dilatation.

Two other animals which were given intracerebral injections of 2 cc. of a 10 per cent suspension made from the cord of this animal did not become paralyzed.

None of the 7 animals that survived the injection of the virus into the adrenal was protected, since every one succumbed to a subsequent intracerebral injection of 0.2 cc. of a 1 per cent virus suspension.

It is thus seen that the injection of the virus into the adrenals did not produce the disease in normal monkeys, which had been fed a complete diet including all the vitamins.

### EXPERIMENT 2

Because of previous success in accelerating the production of paralysis by the addition of paratyphoid-colon bacillus filtrate (enteric toxin) to the virus,[4] 8 other monkeys were operated on, and into the left adrenal of each was injected 0.6 cc. of a virus suspension (from 2 per cent to 10 per cent) in enteric toxin filtrate. One animal which received the injection on Dec. 19, 1934 died on December 31; 1 which had the injection on Feb. 2, 1935 died on February 6; 1 which was given the injection on May 22 had tremor and weakness of the left leg on May 31. Furring was the only reaction seen in the other 5 animals. The latter 5 monkeys and the 1 with weakness of the left leg had no protection, since all 6 succumbed to a subsequent intracerebral injection of 0.2 cc. of a 1 per cent virus suspension.

The lungs of the animal which died on February 5 were massively congested and almost hemorrhagic. There was a large clot in the center of each adrenal. Microscopic examination revealed the center of the injected adrenal to be a mass of red cells. The cells of the cortex were squeezed toward the capsule, and the cytoplasm was swollen and vacuolated. Sections of the lumbar, cervical and bulbar areas of the spinal cord showed some shrinkage of the outlines of the motor cells, but there was no decrease in their number.

Two monkeys were each given intracerebral injections of 2 cc. of a 10 per cent suspension of the cord of the animal which died on February 5. The disease developed in neither one, although both succumbed later to the intracerebral injection of 0.2 cc. of a 1 per cent virus suspension.

An autopsy of the animal which died on Dec. 31, 1934 showed practically normal organs save for slight enlargement of the spleen, obvious dilatation of the small intestine and its vessels and some enlargement of the mesenteric glands. The injected adrenal was normal in size. Microscopically, the cells of the gland were swollen and the cytoplasm was vacuolated. There was no cuffing about the vessels seen in the sections of the lumbar, thoracic or cervical areas of the spinal cord, but the anterior horn cells were decreased in number, shrunken in size and indistinct in outline. Marked infiltration of neuroglia cells was present, but there was only an occasional round cell. There were isolated spots of hemorrhage and

4. Toomey, J. A.: Accelerated Production of Poliomyelitis, Proc. Soc. Exper. Biol. & Med. **31**:1015, 1934.

an increase in the number of capillaries. In brief, a picture of destruction of anterior horn cells was seen, but there was no cuffing and no marked infiltration of round cells.

Each of 2 monkeys was given an injection of 2 cc. of a 10 per cent suspension made from the cord of this animal. Typical poliomyelitis developed in both animals, in 1 in eight and in the other in nine days.

Of 16 monkeys into which poliomyelitis virus was injected by way of the adrenal gland, only 1 became ill with a disease which could be transferred to another animal and then only when enteric toxins were added to the virus.

### EXPERIMENT 3

The cortical tissue of the adrenal gland is rich in lipoids, its lipoidal content being higher than that of any organ or tissue. The adrenal increases in size when a high cholesterol diet is given, and it is stated that this gland is connected with the metabolism of cholesterol. It is said that during pregnancy, when the adrenal also increases in size, the blood cholesterol is found to be increased. This gland is more generously supplied with nerves in proportion to its mass than any other organ of the body.

Two factors are noted. 1. The nerves supplying the adrenal are well medullated as far as the capsule, and well medullated nerves resist the spread of the virus. 2. This gland contains a high percentage of cholesterol, which has been shown to adsorb purified poliomyelitis virus. Perhaps by rendering the medullation deficient these nerves may be made less resistant to the spread of the virus. This deficiency can be effected easily in monkeys by producing rickets in them.

The monkeys used in this experiment were 4 of a group of 17 which for over a period of nine months had been fed a diet deficient in vitamin D until the blood calcium ranged from 10.7 to 11.2 mg. per hundred cubic centimeters and the phosphorus from 1.2 to 1.5 mg. per hundred cubic centimeters. In 3 of the animals fed deficient diets full blown rickets, as determined by roentgen examination, developed. Not quite the same stage of rachitic development was reached in the fourth animal, but the roentgen findings were suggestive. There were 4 control animals which had been fed a diet high in vitamin D. After abdominal section, 0.5 cc. of a 10 per cent suspension of purified virus was injected directly into the medulla of the left adrenal of each animal.

In 3 control animals the disease did not develop, while in 1 there was questionable paresis of some of the muscles of the leg. The disease developed in all 4 of the rachitic animals.

### CONCLUSION

These experiments lend support to the belief (1) that ordinarily virus of poliomyelitis does not spread along well myelinated nerves of healthy Macaca mulatta monkeys and (2) that virus will spread along nerves of vitamin D–deficient monkeys if the virus is simply placed in contact with postganglionic fibers. The presumption is that in the latter animals the preganglionic medullated nerve fibers to the adrenal gland are made deficient and hence more susceptible.

# THERAPEUTIC PROCEDURES FOR SCARLET FEVER

## COMPARATIVE STUDIES

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There is a great difference of opinion as to the efficacy of sulfanilamide in the treatment of scarlet fever. This situation is usual with any new drug, when further experience after its introduction has shown it not to be of great specific value. Reports in the literature vary from that of Le Fevre,[1] who wrote of treating a "large number of patients" in only 1 of whom there developed the usual complications of scarlet fever, such as otitis media, adenitis or mastoiditis, to that of Schwentker and Waghlestein,[2] who actually found more otitic complications in the patients given sulfanilamide than in the controls.

We have just completed a controlled study of 293 patients with scarlet fever admitted to and discharged from the Kingston Avenue Hospital for Contagious Diseases between February and June 1939. The investigation was started in an attempt to determine the value of sulfanilamide and scarlet fever antitoxin, singly and in combination, in combating the initial toxic phase and preventing complications in scarlet fever. We have also included in this report an analysis and summary of the observations of other workers in the field.

Domagk[3] in 1935 demonstrated the efficacy of compounds of sulfanilamide in the treatment of infections produced experimentally in mice with beta hemolytic streptococci. This was confirmed by other observers at about the same time.[4] They believed that the drug acted by inhibiting the growth of streptococci and injuring the organisms in such a way as to permit them to be phagocytosed by the white blood cells.

In 1937 Long and Bliss[5] in a clinical experiment used sulfanilamide in various streptococcic infections and reported the treatment of 8

1. Le Fevre, G.: M. World **56**:660, 1938.

2. Schwentker, F. F., and Waghlestein, J.: Baltimore Health News **15**:41, 1938.

3. Domagk, G.: Deutsche med. Wchnschr. **61**:250, 1935.

4. (*a*) Levaditi, C., and Vaisman, A.: Compt. rend. Acad. d. sc. **200**:1694, 1935. (*b*) Nitti, F., and Borst, D.: ibid. **119**:127, 1933.

5. Long, P. H., and Bliss, E. A.: Para-Aminobenzenesulfonamide and Its Derivatives: Clinical Observations on Their Use in Treatment of Infections Due to Beta Hemolytic Streptococci, Arch. Surg. **34**:351 (Feb.) 1937.

patients with scarlet fever with complete recovery. In that year there also appeared reports by Peters and Havard,[6] Hogarth,[7] Mitman[8] and Patterson.[9] Subsequent publications included those of Sako, Dwan and Platou,[10] Schwentker and Waghlestein,[2] Le Fevre,[1] Wesselhoeft and Smith[11] and Hamilton and Togasaki.[12]

## PROCEDURE

Depending on the severity of illness, each patient admitted was placed in one of three groups, that is, "mild," "moderately severe" or "severe." The following signs were used as a guide in classifying the patients:

Group 1 (mild)—Temperature 100.5 F. or less; toxicity slight or none; no complications.

Group 2 (moderately severe)—Temperature of 101 F. or over; toxicity; complications present.

Group 3 (severe)—Temperature 104 F. or over; marked prostration; complications present.

The treatment given depended on the severity of the illness, as follows:

Patients of group 1, admitted with "mild" scarlet fever, were treated symptomatically.

Patients of group 2, admitted with "moderately severe" scarlet fever, were treated, in rotation, in one of four ways: (1) with sulfanilamide, (2) with scarlet fever antitoxin, (3) with scarlet fever antitoxin and sulfanilamide and (4) with no therapy (control).

Patients of group 3, those who were severely ill, were given one of two forms of therapy: (1) scarlet fever antitoxin or (2) scarlet fever antitoxin and sulfanilamide.

The degree of illness, with subsequent classification and treatment, was determined and recorded by the admitting physician. The antitoxin was given intramuscularly, in the admitting room. The drug therapy was started on the arrival of the patient in the ward. The dose of sulfanilamide given to the patient during twenty-four hours was 1 grain (0.06 Gm.) per pound (0.5 Kg.) of body weight. Up to 60 grains (3.88 Gm.) was given to children and up to 80 grains (5.18 Gm.) to adults. The initial dose was half the estimated daily dose. Equal amounts of sodium bicarbonate were given with the sulfanilamide. A full dose was administered until the temperature was 100 F. or less for four days. Then one half the dose was given the following four days, so that each patient was under the influence of the drug for at least eight days.

Determinations of hemoglobin content and red blood cell counts were done every other day on patients receiving the drug. White blood cell counts and differential studies were made when indicated. Determinations of the concentration of sulfanilamide in the blood were done on the third day.

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6. Peters, B. A., and Havard, R. V.: Lancet **1**:1273, 1937.
7. Hogarth, J. C.: Brit. M. J. **2**:1160, 1937.
8. Mitman, M.: Brit. M. J. **2**:929, 1937.
9. Patterson, D. C.: J. Connecticut M. Soc. **1**:358, 1937.
10. Sako, W.; Dwan, P. F., and Platou, E. S.: Sulfanilamide and Serum in Treatment and Prophylaxis of Scarlet Fever, J. A. M. A. **111**:995 (Sept. 10) 1938.
11. Wesselhoeft, C., and Smith, E. C.: New England J. Med. **219**:747, 1938.
12. Hamilton, P., and Togasaki, Y.: J. Pediat. **14**:655, 1939.

Two hundred and ninety-three patients were studied in this series (table 1). Of these 125 were in group 1 (mild scarlet fever), 154 in group 2 (moderately severe scarlet fever) and 14 in group 3 (severe scarlet fever).

## CLINICAL DATA

*Group* 1.—There were 125 patients in this group. The average age was 8.6 years, and the mean day of the illness on admission was two and nine-tenths. The initial pyrexia was absent in these patients, as on admission to the hospital the temperature was 100.5 F. or less. Signs present on admission were usually a slight rash, associated with a "strawberry" tongue, and a mild angina. A number of these patients were sick at home for several days and on admission to the hospital

TABLE 1.—*Classification of Patients with Scarlet Fever*

| Severity of Illness: | No. of Patients |
|---|---|
| Group 1: Mild | 125 |
| Group 2: Moderately severe | 154 |
| Group 3: Severe | 14 |
| Total | 293 |

TABLE 2.—*Clinical Data on Group 1*

| | | |
|---|---|---|
| Number of patients | | 125 |
| Average age, years | | 8.6 |
| Mean day of disease on admission | | 2.9 |
| Complications during stay in hospital | | 13 |
| Adenitis | 8 | |
| Otitis | 2 | |
| Tonsillitis | 2 | |
| Ethmoiditis | 1 | |
| Mean duration of stay in hospital, days | | 21.7 |

were afebrile. The large number of patients with mild scarlet fever (41 per cent of all admissions) denotes the benign nature of the disease prevalent today.

During the stay in the hospital in 13 patients, or 10.4 per cent of this group, complications developed; among them were 8 patients with adenitis. Four of these received sulfanilamide on development of the complication. Four did not receive the drug. The course of the adenitis seemed to be unaffected by the therapy, as noted by the duration of the febrile state and the swelling of the affected glands.

The data for this group are presented in table 2.

*Group* 2.—The patients in this group were divided into four subgroups, of which three received in rotation a different form of therapy and the fourth acted as a control, with no therapy. Uniformity was achieved in the different groups, as evidenced by the approximation

of the age as well as the mean day of the disease on admission. The seasonal factor was eliminated, because these patients were admitted during a five month period.

There were 154 patients in this group. The patients receiving combined therapy (subgroup 2c) apparently had a shorter duration of initial pyrexia in the hospital, but this advantage was offset by the longer duration of the disease prior to admission to the hospital as compared to subgroups 2a, 2b and 2d. In the patients receiving no therapy (subgroup 2d) the greatest number of complications developed. The data for this group are presented in table 3.

*Group* 3.—There were 14 patients in this group. These patients were not given therapy in the form originally planned. When this study

TABLE 3.—*Clinical Data for Group 2*

| | 2a Sulfanilamide | 2b Scarlet Fever Antitoxin | 2c Sulfanilamide and Scarlet Fever Antitoxin | 2d No Therapy |
|---|---|---|---|---|
| Number of patients (total 154) | 41 | 40 | 31 | 42 |
| Average age in years | 7.4 | 10.5 | 8.6 | 7.8 |
| Mean day of disease on admission | 2.6 | 2.8 | 3.0 | 3.1 |
| Mean duration of initial pyrexia while in hospital, days | 2.6 | 2.5 | 1.9 | 2.5 |
| Number of complications | 6 | 8 | 5 | 13 |
| Percentage of complications | 14.6 | 20 | 15.7 | 30.9 |
| Adenitis | 3 | 2 | 3 | 6 |
| Otitis media | 2 | 4 | 2 | 5 |
| Arthritis | .. | 1 | .. | .. |
| Nephritis | .. | 1 | .. | .. |
| Tonsillitis | .. | .. | .. | 1 |
| Mastoiditis | 1 | .. | .. | .. |
| Ethmoiditis | .. | .. | .. | 1 |
| Mean duration of stay in hospital, days | 25.4 | 21.6 | 23.8 | 25.5 |

was begun, we were under the impression that sulfanilamide was of greater value in scarlet fever than subsequent observations have shown it to be. The patients in this group were seriously ill, and we wanted to give them every possible aid; so a large majority were given sulfanilamide. Another change in plans was the prescribing of sulfapyridine to patients with pulmonary complications. Table 4 briefly outlines the course of these patients.

## COMMENT ON THERAPEUTIC EFFICACY

The early claims for the therapeutic success of sulfanilamide in the treatment of scarlet fever have not been substantiated by later observations. This failure may be explained by the fact that several strains of streptococci are not influenced by this drug, or it may challenge the theory of the primary association of this organism with scarlet fever.

TABLE 4.—*Clinical Data for Group 3*

| Case No. | Day of Illness | Age, Yr. | Complication on Admission | Duration of Initial Pyrexia | Treatment | Course in Hospital |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | Tonsillitis | 5 | Scarlet fever antitoxin and sulfanilamide | Adenitis, otitis media and mastoiditis (unilateral) developed, with subsequent operation; 87 days in hospital; hemoglobin fell from 74% to 61%; concentration of sulfanilamide in blood, 3.3 mg. per 100 cc. |
| 2 | 6 | 7 | Otitis media | 5 | Scarlet fever antitoxin and sulfanilamide | Mastoiditis (unilateral) with subsequent operation; 69 days in hospital; hemoglobin changed from 69 to 55%; concentration of sulfanilamide in blood, 5 mg. per 100 cc. |
| 3 | 8 | 10 | Otitis media; arthritis | 7 | Scarlet fever antitoxin and sulfanilamide | Bilateral mastoiditis developed, with subsequent operation; 77 days in hospital; hemoglobin fell from 68% to 48% |
| 4 | 3 | 9 | Petechial rash; tonsillitis | 7 | Scarlet fever antitoxin and sulfanilamide | Adenitis; 25 days in hospital; hemoglobin fell from 80% to 65%; concentration of sulfanilamide in blood, 6.5 mg. per 100 cc. |
| 5 | 5 | 7 | Tonsillitis | 7 | Scarlet fever antitoxin and sulfanilamide | Otitis media; 21 days in hospital; hemoglobin fell from 72% to 55%; concentration of sulfanilamide in blood, 7 mg. per 100 cc. |
| 6 | 3 | 8 | Tonsillitis | 1 | Scarlet fever antitoxin and sulfanilamide | Adenitis; 25 days in hospital; hemoglobin 88% on admission, fell to 70% at discharge; concentration of sulfanilamide in blood, 1.8 mg. per 100 cc. |
| 7 | 1 | 5 | Tonsillitis | 9 | Scarlet fever antitoxin and sulfanilamide | Adenitis; 20 days in hospital; hemoglobin fell from 62 % to 54%; concentration of sulfanilamide in blood, 3.5 mg. per 100 cc. |
| 8 | 2 | 8 | None | 5 | Scarlet fever antitoxin and sulfanilamide | No complications; 21 days in hospital; hemoglobin fell from 87% to 67%; concentration of sulfanilamide in blood, 6.4 mg. per 100 cc. |
| 9 | 2 | 12 | None | 2 | Scarlet fever antitoxin and sulfanilamide | Temperature elevated on 4th day with no apparent cause found; administration of sulfanilamide discontinued; temperature returned to normal in 3 days; hemoglobin changed from 68% to 70%; concentration of sulfanilamide in blood, 6.2 mg. per 100 cc. |
| 10 | 3 | 10 | None | 10 | Scarlet fever antitoxin | 20 days in hospital; no complications |
| 11 | 4 | 12 | None | 8 | Sulfanilamide and convalescent serum | Transfusion of 100 cc. of convalescent serum given (patient sensitive to horse serum); no complications; 27 days in hospital; hemoglobin fell from 70% to 60%; concentration of sulfanilamide in blood, 4.2 mg. per 100 cc. |
| 12 | 5 | 5 | Otitis media; pneumonia | 2 | Sulfapyridine and scarlet fever antitoxin (drug discontinued on 3d day) | Effusion and empyema developed in hospital; thorocotomy done; hemolytic streptococci isolated from chest fluid; hemoglobin fell from 79% to 53%; concentration of sulfanilamide in blood, 11.2 mg. per 100 cc.; hospital stay, 32 days |
| 13 | 4 | 5 | Otitis media; pneumonia with effusion | 14 | Scarlet fever antitoxin and sulfapyridine with oxygen | Empyema with subsequent thorocotomy; 150 days in hospital; administration of drug discontinued on 6th day in hospital |
| 14 | 4 | 2 | Adenitis | 1.5 | Scarlet fever antitoxin and sulfanilamide | Died of sepsis and pneumonia 36 hours after admission |

*Effect of Drug on Initial Period of Pyrexia.*—Sulfanilamide has little or no effect on the intial phase of the disease (table 5). This has been our experience and the experience of most observers.[13] This general conception is different from that of Patterson, who reported a drop in fever within thirty-six or forty-eight hours in patients treated with sulfanilamide, and of Le Fevre, who noticed that the "period of fever in the majority of cases was lessened." Protocols were not given in either report, nor was the use of controls mentioned.

TABLE 5.—*Effect of Therapy on Duration of Initial Pyrexia*

| | Duration of Pyrexia with Various Types of Therapy in Days | | | |
|---|---|---|---|---|
| Source | Sulfanilamide | Scarlet Fever Antitoxin | Sulfanilamide and Scarlet Fever Antitoxin | No Therapy |
| Kingston Avenue Hospital | 2.6 | 2.5 | 1.9 | 2.5 |
| Peters and Havard | 3.3 | ... | ... | 2.5 |
| Hogarth | ... | 3.9 | 3.9 | 3.7 |
| Schwentker and Waghlestein | 4.4 | 4.0 | ... | 5.2 |
| Sako, Dwan and Platou* | 6.0 | ... | ... | 6.0 |
| Wesselhoeft and Smith | 2.6 | ... | ... | 3.0 |

* Included days of fever prior to admission.

TABLE 6.—*Influence of Sulfanilamide on Incidence of Complication in Scarlet Fever*

| | Percentage of Patients with Complications on Basis of Type of Therapy | | | |
|---|---|---|---|---|
| Source | Sulfanilamide | Scarlet Fever Antitoxin | Scarlet Fever Antitoxin and Sulfanilamide | No Therapy |
| Kingston Avenue Hospital | 14.6 | 17.3 | 15.7 | 30.9 |
| Hogarth | .... | 23.0 | 21.9 | 26.9 |
| Peters and Havard | 35.0 | .... | .... | 56.0 |
| Hamilton and Togasaki | 10.6 | 13.6* | .... | .... |
| Wesselhoeft and Smith | 66.0 | .... | .... | 72.0 |
| Schwentker and Waghlestein | 23.6 | 13.7 | .... | 16.6 |
| Sako, Dwan and Platou | 8.0 | .... | .... | 41.0 |

* Convalescent serum was given.

The initial toxic phase was noticeably and promptly shortened in the series of patients given antitoxin or convalescent serum. However, the duration of the rise in temperature was but slightly affected. The malaise seemed to be aggravated in the patients receiving sulfanilamide. We could detect those under the influence of the drug by their listlessness and lethargy.

*Effect of Drug on Incidence of Complications.*—The efficacy of sulfanilamide in preventing complications when given during the

13. Schwentker and Waghlestein.[2] Peters and Havard.[6] Hogarth.[7] Mitman.[8] Patterson.[9] Sako, Dwan and Platou.[10]

eruptive stage is questionable. Some observers [14] believe that it has no effect. Others [15] have apparently obtained beneficial results with its use (table 6).

Hogarth [7] in a study of 350 cases found that the use of the drug did not influence the incidence of complications.

Peters and Havard [6] studied 150 patients to whom the drug was given and a similar number of controls. Fifty-six of the latter received antitoxin. They found that while the total number of complications was the same, the number of patients affected was less in the group given drug therapy. The percentage of complications was reduced from 56 per cent to 35 per cent. Wesselhoeft and Smith in analyzing the aforementioned figures found that the difference was due to a greater number of patients showing albuminuria, "endocarditis" and "rheumatism" in the group used as controls. They expressed the belief that the meaning of these complications has been misinterpreted. Transitory albuminuria is insignificant in febrile reactions. The interpretation of the term "endocarditis" is questionable, as the disorder occurs in less than 0.5 per cent of cases of scarlet fever (in Peters and Havard's series it occurred in 6 per cent of the cases), and "rheumatism" may be a sign of serum reaction. Complications characteristic of the disease, such as adenitis and otitis media, occurred in the same percentages in the treated and in the untreated group.

Mitman [8] reported treating 355 patients, with no apparent reduction in the incidence of complications. No protocol or evidence of control was given in the report.

Patterson [9] in reporting the treatment of over 200 patients with scarlet fever with drug therapy mentioned that "complications have been seen but rarely." There were a few instances of swollen cervical glands but none of otitis media.

Sako, Dwan and Platou [10] reported a great diminution in the incidence of complications in the group given the drug in comparison with the control group. However, examination of their protocol reveals that 11 per cent of their patients had nephritis. This is contrary to the incidence of nephritis in scarlet fever, which has been 1 per cent (Stinson).

Schwentker and Waghlestein [2] in a study of more than 300 cases reported an actual increase in number of complications in the group given sulfanilamide over that in two control groups.

Le Fevre,[1] in treating a "large number" of patients with scarlet fever, found that "not one patient developed otitis media, mastoiditis,

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14. Long and Bliss.[5] Hogarth.[7] Patterson.[9] Hamilton and Togasaki.[12]

15. Levaditi and Vaisman.[4a] Nitti and Borst.[4b] Peters and Havard.[6] Mitman.[8] Sako, Dwan and Platou.[10] Wesselhoeft and Smith.[11]

nephritis, or carditis." Cervical adenitis developed in only 1 and that in a mild form.

Wesselhoeft and Smith [11] compared their results with those of Peters and Havard and Schwentker and Waghlestein and arrived at the conclusion that sulfanilamide administered in the usual dosage during the initial stage of the disease did not appreciably reduce the incidence of adenitis, otitis media or mastoiditis.

Hamilton and Togasaki [12] studied the effect of sulfanilamide in comparison with that of pooled convalescent serum. They found that in 13.6 per cent of the patients treated with serum complications developed, while 10.6 per cent of those treated with the drug were affected.

In examining our protocols we found that the effect of sulfanilamide in preventing complications is not impressive. The untreated patients in group 2 (moderately severe scarlet fever) showed a greater incidence of complications than those given specific therapy. However, it has been pointed out [9] that wide variations often exist in any series of 100 cases or less. This variation may account for the contradictory results obtained by the various authors.

All the patients severely ill were given antitoxin. In addition, 11 patients were given sulfanilamide and 2 were given sulfapyridine. Although no controls were used, examination of the records of this group reveals some information as to the value of these drugs. The initial pyrexia was not influenced by drug therapy, as evidenced by the prolonged fever in almost all cases.

In 8 of the 10 patients receiving sulfanilamide complications developed. In spite of intensive drug therapy in 3 of these patients mastoiditis developed and they subsequently came to operation. The administration of sulfapyridine to both the patients to whom it had been given was discontinued. The reactions noted were an intensification of the malaise and a marked fall in hemoglobin content. One patient, a child who had been given sulfanilamide, died of sepsis and bronchopneumonia. Thus we feel that the use of sulfanilamide does not greatly influence the course of severe scarlet fever.

*Effect of Sulfanilamide in Treatment of Complications.*—In group 1 (mild scarlet fever) of our study there were 8 patients with cervical adenitis, which developed between the seventh and the fourteenth day of illness. Four of these patients were treated with sulfanilamide; the other 4 were not given the drug. There was no appreciable difference in the course of the complication as evidenced by the duration of the fever as well as by the extent of the adenitis.

Hogarth [7] in his series gave the drug during the convalescent period as well as in the initial toxic phase. He, too, noted no appreciable difference in the complications among the group treated with the drug in comparison to the control group.

*Concentration of Sulfanilamide in the Blood.*—The dosage recommended by Long and Bliss resulted in a concentration in the blood of from 4 to 8 mg. or sulfanilamide per hundred cubic centimeters. This concentration, according to the authors, was essential for proper therapeutic effect. In examining the protocols of the papers analyzed we find that in all but 1 instance [6] the investigators employed adequate doses.

In our series two subgroups, 2a and 2c, of the group of patients with a moderately severe illness were given sulfanilamide. The former were given the drug alone, while the patients in the latter subgroup were given antitoxin in addition. Determinations of the concentration of sulfanilamide in the blood were done on the third day. In group 2a the mean average concentration was 4.82 mg. per hundred cubic centimeters of blood and varied from 1.6 to 7.1 mg. In group 2c the average concentration was 5.02 mg. and varied from 1.7 to 12.9 mg. No mention was made by other observers of the concentrations of the drug in the blood.

Values for hemoglobin were determined every other day on those patients receiving the drug. From the time of admission to the hospital until drug therapy was discontinued the average mean fall in hemoglobin content for group 2a was 6.1 per cent and for group 2c 5.9 per cent. There was no definite relation between the fall in hemoglobin content and the concentration of the drug in the blood. The drop in hemoglobin content might be accounted for by the infectious process. However, in several cases there was a marked drop in hemoglobin content, notably of 24 per cent and 33 per cent. One of these cases is worth reporting.

L. F., a Negro boy aged 12, was admitted on April 10, 1939 to the scarlet fever service, classified as having moderately severe scarlet fever. Sulfanilamide therapy was begun soon after admission. On April 12 the hemoglobin content was 68 per cent and the red blood cells numbered 3,500,000 per cubic centimeter of blood. The concentration of the drug in the blood on April 13 was 6.2 mg. per hundred cubic centimeters. The next day the hemoglobin content fell to 50 per cent, and the red blood cell count was 3,000,000. The administration of the drug was discontinued. In spite of this, three days later the hemoglobin content had fallen to 38 per cent. On the same day a determination of the concentration of the drug in the blood was 3.4 mg. The icteric index was 3.1. On April 19 the hemoglobin level was 35 per cent and red blood cell count 2,400,000. The patient was pale but comfortable. At no time was there any evidence of jaundice, rash or febrile reaction.

Soon after anemia set in, therapy was instituted. The patient was given 3 grains (0.19 Gm.) of ferrous sulfate three times a day; he was placed on a hematonic diet, and 1 vial of liver extract was given intramuscularly daily. Blood transfusion was not done. Three weeks after entering the hospital the patient was discharged, with almost the same blood picture as that present on admission and evidently none the worse for the experience.

## CONCLUSIONS

A study of the available literature to date on the use of sulfanilamide in scarlet fever is inconclusive and contradictory. However, certain conclusions can be drawn from the various writings, including our own.

1. The effect of sulfanilamide in scarlet fever is not as beneficial as it has proved to be in other streptococcic infections, such as erysipelas or streptococcic meningitis.

2. Sulfanilamide given in proper doses during the initial stage of scarlet fever does not diminish the toxicity or duration of the fever. Frequently the malaise is intensified by the drug.

3. Sulfanilamide therapy reduced the incidence of complications in seven of the reports studied but had no effect or a deleterious one in four other series. In view of the prevailingly favorable opinion and the availability of the drug, sulfanilamide should be given in severe and moderately severe scarlet fever until further evidence to the contrary is produced.

4. The scarlet fever prevalent today is mild. This observation was noted by almost all workers in the field and evidenced further in our series by the large number of patients (42 per cent) who had temperatures of 100.5 F. or less on admission.

5. Scarlet fever antitoxin or convalescent serum successfully combats the initial toxic phase and should be given early in the disease.

6. Sulfanilamide is not entirely harmless and should be given under supervision. Frequent studies of the blood are indicated.

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# ETIOLOGY OF MULTIPLE DEFORMITIES

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## I. ETIOLOGY OF DYSOSTOSIS MULTIPLEX (PFAUNDLER-HURLER)

Dysostosis multiplex is a combination of an extraordinarily large number of signs which appear entirely unrelated. The theory to be evolved concerning the etiology of this disease may deserve a wider interest because it seems to be applicable to a considerable number of mysterious syndromes. Moreover, it may lead to a new conception of the etiology of single deformities. The application of this theory to dysostosis multiplex should, therefore, be considered as a test of usefulness.

A full description of dysostosis multiplex and a review of the 23 cases known so far in the literature were published recently. The signs, which were classified in three groups, will therefore be mentioned here only briefly. The first group concerned the skeletal and soft parts of the head and consisted chiefly of a deformity of the skull (oxycephaly, scaphocephaly), hydrocephaly, low-set ears, cloudiness of the corneas, poor hearing and enlarged hypophysis. The second group, described under the heading "endocrine disturbances" (hypothyroidism), comprised disproportionate dwarfism, dry puffy skin, idiocy, saddle nose, multiple hernias, crura valga, pedes plani and diminished excretion of water. Atrophy and fibrosis of the thyroid were found on histologic examination. Of the anomalies of the osteoarticular apparatus, which made up the third group of signs, the most common were clumsiness of the bones with multiple irregularities of shape and structure, restricted movement of the large joints, Sprengel's deformity, lordosis and claw hands. The upper extremities were more involved than the lower ones. Enlargement of the spleen and liver was often present. A common feature was cutis laxa over the neck and extremities, to which I attribute great significance.

Apart from a suggestion of Tuthill, to be discussed later, nothing is known about the etiology of this interesting disease. Ullrich, however, attempted to apply the remarkable experimental results of Bagg and Little to a conception of the etiology of some other multiple human deformities.

In 1924 Bagg and Little submitted the ovaries of mice to roentgen irradiation; the mice produced progeny many of which suffered from

malformation of the limbs—clubfoot, polydactyly and similar malformations—and anomalies of the eyes. Although these deformed mice had not themselves been submitted to roentgen irradiation, they produced a high proportion of young with the same malformations. The acquired anomalies proved, therefore, to be inheritable, and pathologic descendants could be bred through an indefinite number of generations. The experimenters further found that the malformations were caused by blebs appearing in the subcutis of the affected limbs at an early embryonic age.

Bonnevie has given a satisfactory explanation for the development of these blebs. She found that they are formed of cerebrospinal fluid

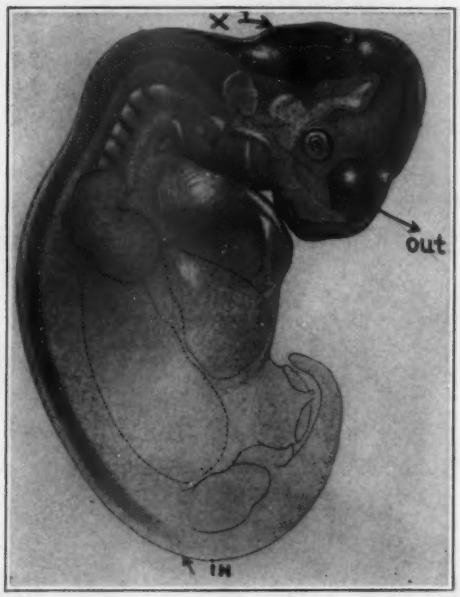


Fig. 1.—Area membranacea in a pig embryo, indicated by *X*. (Figures 1 to 4 are taken from Weed, L. H.: The Development of the Cerebrospinal Spaces in Pig and Man, Publication 225, Carnegie Institution of Washington, 1916.)

which had escaped into the subcutis through the foramen anterius (Weed), called the area membranacea anterior, a gap in the roof of the developing fourth ventricle.

This area was found by Weed by replacing the cerebrospinal fluid of living pig embryos with a solution of potassium ferrocyanide and iron-ammonium citrate in equal parts. In the treated embryo a well circumscribed blue spot appeared at the roof of the fourth ventricle. Its localization is shown in a few pictures from Weed's classic monograph. It corresponds to the area marked *X* in figure 1. The general

topography of the area membranacea is shown in the rectangular space marked off in figure 2, which is a median sagittal section from a pig embryo of 13 mm. Figure 3 shows the same area in a transverse section from a pig embryo of 23 mm.

The dimensions of the area membranacea anterior in a pig embryo of 13 mm. are 0.45 by 0.6 mm., in a human embryo of 14 mm. they are 1.25 by 1.1 mm. In figure 4 a higher magnification shows the sharp delimitation of the area from the surrounding tissue and its high differentiation from the adjacent ependyma (chick embryo of one hundred and twenty-one hours' incubation). The ventricle here is separated from the periaxial tissue only by a single layer of cells.

The area membranacea under normal circumstances regresses and finally disappears, owing to the caudal growth of the cerebellum and the

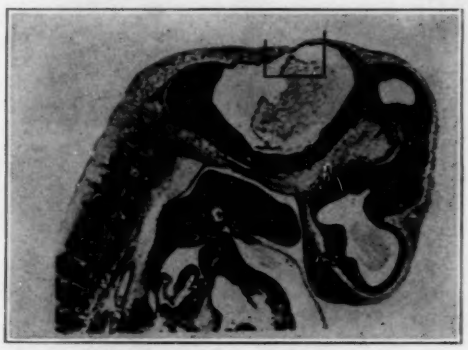

Fig. 2.—A median sagittal section from a pig embryo of 13 mm., showing the general topography of the area membranacea (in the square). (From Weed.)

enlargement of the choroid plexus, but while present it functions as a physiologic membrane; it is here that the transit of cerebrospinal fluid from the ventricle to the periaxial tissue takes place. The permeability of this area was studied recently by Cohen and Davies in chick embryos. Figure 5 shows how the dye (*S*) injected into the ventricular system had invaded the dorsal medullary mesenchyme. The site of escape of the fluid was the anterior membranous area (*A. M.*), which is much thinner than the surrounding ependymal layers. From stages of 24 mm. and over the lower membranous area is the only one of significance for the total passage of fluid (*P. M.*, fig. 5).

The conditions in human embryos are much the same as those described in chick and pig embryos. The area membranacea seems to exist in all vertebrates before Magendie's foramen is formed. The cerebrospinal fluid that escapes through it spreads over the cerebral surface and by so doing forms the subarachnoid space.

Fig. 3.—Transverse section from a pig embryo of 23 mm., showing the area membranacea (in the closed square). (From Weed.)

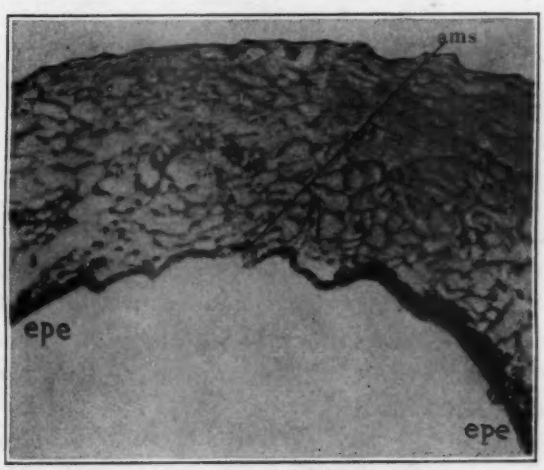


Fig. 4.—Area membranacea anterior in a chick embryo of one hundred and twenty-one hours' incubation, showing its sharp differentiation from the adjacent ependyma (*epe*). (From Weed.)

In tne tribe of irradiated mice of Bagg and Little the escaping fluid was greatly increased and passed into the subcutaneous tissue closely adjacent to the roof of the fourth ventricle. The cerebrospinal fluid that thus escaped began to sink, following the path of least resistance but influenced in its course by such factors as the tension of the skin and the shape of the embryonic surface. An accumulation of fluid occurred especially in such hollow parts and concavities of the body as the root of the nose, the orbits or the blind sacs of the limb buds because it was prevented from sinking farther. An increase of fluid pressure consequently developed at such points. The cerebrospinal fluid thus collected formed the "blebs" of Bagg and Little. The fluid may be reabsorbed by the tissues without leaving a trace or it may act as an irritant and provoke a transudation, with subcutaneous extravasation of blood. Such

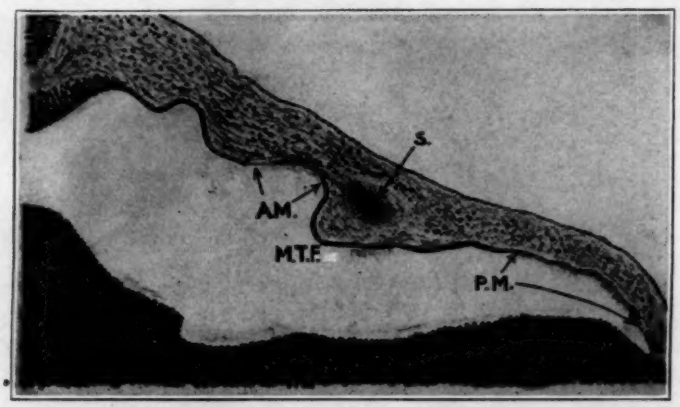


Fig. 5.—Results of injection of dye into the ventricular system of a chick embryo. The dye invaded the dorsal medullary mesenchyme (*S*). The site of escape, the anterior membranous area, is indicated by *A. M.;* the posterior membranous area by *P. M.,* and the median transverse fold by *M. T. F.* (From Cohen, H., and Davies, S.: The Development of the Cerebrospinal Fluid Spaces and Choroid Plexuses in the Chick, J. Anat. **72**:23, 1937.)

increased pressure, followed probably by some change in the physical and chemical conditions of the young tissue, may damage the sensitive mechanism of the developing organs and upset their balance.

By exact study of the subcutaneous path taken by the cerebrospinal fluid, Bonnevie was able to explain every detail of the final deformities of her animals. She found the narrowed palpebral space to be the most common anomaly because of the preference for bleb formation in the face. Sometimes clouding of the corneas was observed. The next most common anomaly was deformity of the forefeet in the form of syndactylism, with various developmental defects of the skeleton. The

deformities were mostly unilateral on account of asymmetry of the shoulder line, which diverted the bleb to one side. The hindfeet were less affected, being farther away from the skull.

The foramen anterius was found also in human embryos (Bonnevie), with strong indication of the existence of blebs of cerebrospinal fluid, associated with anomalies of the fingers and toes. The evidence given by Ullrich also suggests that the bleb of cerebrospinal fluid is responsible for the anomalies described by him. One of his patients displayed a cystlike pouch in the skin of the neck; others, cutis laxa in the same region, and the last one, pterygium colli. In all of his 5 cases there was a deep setting of the deformed ears combined with postnatal edema of the extremities.

Ullrich mentioned also an anomaly consisting of symbrachydactylia and congenitally defective movements of the eyes and eyelids, often with defects of the pectoral muscle. This anomaly combined with a clavicular defect and Sprengel's deformity has been recorded in more than 50 cases.

An interesting combination of congenital paresis of the facial nerves with deformities of the upper extremity and the ears is explained by the fact that the foramen anterius in an embryo of 7 to 8 mm. lies exactly opposite the nuclei of the facial and abducens nerves. The lesion of the extremities is believed to be due to direct local action of the bleb of cerebrospinal fluid.

In the text that follows an attempt will be made to explain the origin of dysostosis multiplex in the light of this new conception, which shall be called hereafter the "bleb theory." It can be said at the outset that there is hardly any sign of dysostosis multiplex that has not been produced experimentally in the mice of Bagg and Little or that has not figured among the signs presented in Ullrich's cases, which may be explained on an analogous basis.

The fact that deformity of the skull and clouding of the corneas were present in each of the known 23 cases, while the other anomalies varied in degree and localization, points toward the skull as the seat of the primary lesion. The early hydrocephalus, the protrusion of the eyes, the high palate and the constriction of the nasal cavity are all proof that the cranial base was involved in the original derangement. My roentgenographic findings support such an assumption; the results of the autopsy in Tuthill's case confirm it.

The presence of hydrocephalus does not of itself prove the correctness of the bleb theory, though it may be considered as a *conditio sine qua non*. It seems reasonable to assume that increased intramedullary pressure offers good opportunities for the foramen anterius to keep patent. It acts as a kind of safety valve against the pressure, the whole area being very thin at a certain stage of development, as seen in figures

2 and 5. There are some findings suggestive of the assumption that in dysostosis multiplex the superfluous liquor does escape through the patent foramen into the subcutaneous tissue and that it does sink into the subcutis of the periphery. Cutis laxa was described in several cases of dysostosis multiplex. Its significance, especially in the region of the neck, with regard to other deformities has been pointed out by Ullrich. He took it for a dilatation of the skin in early embryonic life by the escaped cerebrospinal fluid, as previously described. It would be hard to explain its presence in dysostosis multiplex as sheer coincidence.

As early as the first reported case of dysostosis multiplex (Pfaundler and Hurler) one finds the description of cutis laxa in the region of the back and breast. In the second case to be reported Hurler mentioned that the skin was lax and could be lifted in big folds. Putnam and Pelkan made a similar observation. They found cutis laxa over the thighs, backs of the hands, axillary region and neck. Helmholz and Harrington described their finding as follows: "The skin over the occiput was thickened and felt spongy." The excessive weight (4.5 Kg.) of their patient at birth cannot well be ascribed to hydrocephalus alone because an excess of 25 per cent of the normal total body weight, if localized in the head, would not have resulted in a viable child. It is therefore reasonable to assume that the 1 Kg. of overweight was distributed under the "thickened and spongy" skin, which peeled after birth. In this instance one can practically follow the route of the cerebrospinal fluid from the hydrocephalic head to the neck and from there to the lower extremities.

To appreciate the significance of the cutis laxa, one has to remember that it is a relatively rare anomaly. In spite of that, it was found in 3 of 23 cases of dysostosis multiplex. If one accepts folding eyelids and flabby cheeks as an equivalent of cutis laxa, one can say that it was present in the majority of cases. Its presence in just those parts of the body where it is to be expected according to the experiments with mice is a strong support of my view. It must be admitted, however, that it is not an absolute proof of the bleb theory. On the other hand, by the nature of the deformity one cannot possibly offer any more proofs: One may be fortunate enough to find an embryo with blebs, but such an embryo will be without signs of dysostosis multiplex, which, after all, can only be a late result of the blebs; or one may find the results, the signs of dysostosis multiplex, and traces of the blebs. I think it is hard to explain the cutis laxa, postnatal edema and peeling of the limbs otherwise than as such traces. Ashby also expressed the opinion that "it is perhaps more than a coincidence that in several cases the weight at birth has much exceeded the normal."

After leaving the subarachnoid space the cerebrospinal fluid first reaches the surface of the neck and accumulates there in the hollow between the head and the body, hence the cutis laxa of the neck. With increasing fluid pressure it spreads toward the face, the back and the more developed upper and less developed hindlimb buds. Arriving at the facial surface, it accumulates in the deepest cavities and skin pouches, in the orbits, eyelids and lips. It interferes with the normal development of the eye, keeping it at a primitive stage, hence clouding of the cornea; it causes sagging of the eyelids, flabbiness of the cheeks and enlargement of the lips. It interferes with the normal position of the external ear. The swelling in the back will prevent the shoulder blades from sinking into their normal position, a defect described also in symbrachydactylia. They stop at the level corresponding to that typical of the sixth embryonic week, hence Sprengel's deformity. The bleb of cerebrospinal fluid may disturb the normal development of the vertebral bones or muscles of the back, leading to spinal deformities or the development of the abdominal wall, resulting in a diastasis of the abdominal rectus muscles and the formation of umbilical and inguinal hernias.

From the trunk the cerebrospinal fluid is diverted first toward the upper limb buds, these being nearer the head and more advanced in development. The normal growth of bones and articulations will be hindered, causing contractions and bone deformities. The strongest pressure is exerted at the ends of the phalanges, where the fluid cannot proceed any farther; hence the deformities accentuated toward the phalangeal ends (claw fingers).

By following the route of the cerebrospinal fluid as far as the toes, one is able to understand all the anomalies summarized before under "skull" and "osteoarticular apparatus," especially if one accepts tentatively the fifth to sixth embryonic week as the teratogenic period of dysostosis multiplex. It is of interest to point out that these anomalies are relatively superficial structures, with the exception of those relating to the skull. This holds true especially if one realizes that at the fifth to sixth week the bone system in the limb buds is just at the stage of what one may call crystallization. One may get a correct picture of the action of the bleb if one compares the process to a volcanic eruption, in which lava flowing over vast territories of land devastates everything in its way but keeps to the surface of the earth; the lava is comparable to the cerebrospinal fluid and the crater to the foramen anterius.

The explanation of the signs considered to be endocrine in origin is not so simple. These signs simulate hypothyroidism to a great extent without responding, however, to thyroid treatment and without including a delay in ossification. From the histologic picture it seems nevertheless justified to recognize the thyroid as responsible, directly or indirectly.

for the endocrine disturbance. There are two ways in which the thyroid can be affected by the bleb. First, the cerebrospinal fluid may, on its way from the back to the neck, exert a direct pressure on the gland. Such a selective damage of only one organ deriving from the craniopharyngeal pouch is hardly possible. The indirect way, via hypophysis or hypothalamus, is more likely. The shape of the cranial base and the signs of an early hydrocephalus indicate that the hypophysial region was under increased pressure and could consequently be damaged. The interrelation between thyroid and hypophysis is common knowledge, and a dysfunction of the latter, which was proved in my 2 cases, gives a satisfactory explanation for hypothyroidism in dysostosis multiplex. By accepting the hypothesis of hypophysial dysfunction one finds a plausible explanation for all the signs of dysostosis multiplex. They are all referred to one single cause: an anomalous escape of cerebrospinal fluid into the subcutis and adjacent tissues of the periphery in early embryonic life through the foramen anterius.

In a recent paper Ashby and associates reported histologic changes in 2 cases of dysostosis multiplex which were to a great extent similar to those reported by Tuthill. These authors claimed that the changes resemble in the closest degree those of the juvenile form of amaurotic idiocy. The view is expressed that notwithstanding the failure to find histologic evidence of derangement of lipoid metabolism outside the nervous system, dysostosis multiplex must be accepted as a manifestation of such a pathologic process and consequently belongs to the group of lipoidoses.

I do not think that such a generalizing statement is justifiable from findings restricted to the brain. But granted that further investigation should confirm Tuthill's opinion, it is by no means in contradiction to the bleb theory. If the view of Raab is correct that a pituitary-hypothalamic mechanism controls the lipoid metabolism, then a derangement of the latter could easily be due to a lesion of the cerebral basis and be of the same order as the pathologic water metabolism described in my 2 cases of dysostosis multiplex.

## II. ETIOLOGY OF A GROUP OF SYNDROMES AKIN TO DYSOSTOSIS MULTIPLEX

An attempt was made in the first part of this paper to show that all the signs of dysostosis multiplex could be explained, in spite of their number and apparent diversity, by the bleb theory. A closer study of multiple deformities made me believe that there is a group of other syndromes which has much in common with dysostosis multiplex. I shall now consider how far it is possible to extend the bleb theory to the

pathogenesis of these syndromes analogous in their manifestations and whether they may be coordinated into one system.

I am aware that it may seem premature to attempt a synthesis before the analysis of the components is complete. Most of the syndromes to be discussed are of unknown origin; records of autopsies are scanty or missing. My attempt to bring them into a system is made with the conviction that a synthetic treatment of the subject may encourage the analytic study of the single syndromes from a new angle. They have been described in the past as clinical entities on a purely morphologic basis.

The syndromes to be discussed are: (1) oxycephaly (Virchow), (2) acrocephalosyndactyly (Apert), (3) dysostosis craniofacialis (Crouzon), (4) Laurence-Moon-Biedl syndrome, (5) Morquio's disease, (6) pleonosteosis familiaris (Léri), (7) mongoloid idiocy, (8) craniocarpotarsal dystrophy and (9) H. H. Turner's syndrome. Nearly all these syndromes have in common an incomprehensible combination of some anomaly of the skull with one or another deformity of the extremities. In some of them the cranial deformity is the dominant feature; in others it is the peripheral anomalies. This combination has puzzled many scientists in the past, and not much has been added to the knowledge. One of the most interesting theories advanced is that of Babes, who observed that a malformation of the extremities occurred when the base and the upper part of the facial portion of the skull were abnormally developed but not when the malformation was limited to other parts of the skull. Babes concluded erroneously that there must be in the region of the cranial basis a "trophic center" that controls the normal growth of the extremities. Babes was uncertain of the location of this "center." Though his observations were correct, his final conclusions regarding the trophic center, for which he has offered no proof, were unjustified. But there is no doubt that there is a connection between pathologic processes of the cranial basis and malformations of the rest of the body, especially of the face, eyes and limbs.

The foregoing nine syndromes will be described now and compared with dysostosis multiplex; their etiology will be discussed later.

Oxycephaly is a deformity of the skull secondary to premature synostosis of the cranial sutures. The skull expands at points of least resistance (usually the anterior fontanel). In true oxycephaly all sutures, cranial and facial, are fused. The apex is near or at the bregma. The skull is abnormally high, with a steeply rising forehead and widening of the transverse and narrowing of the anteroposterior diameter. The temporal regions bulge; the orbits are shallow and, consequently, the eyeballs protrude. The maxillary and zygomatic bones are poorly developed; the accessory sinuses are small or absent;

the palate is narrow; there is no diploe. The temporal venous channels are dilated in compensation for the narrowed foramens of the cranial basis. The sella turcica is narrow.

In all patients with dysostosis multiplex a deformity of the skull was present. It was often oxycephaly but sometimes scaphocephaly or trigonocephaly. Study of the roentgenograms published with my 2 cases of dyostosis multiplex reveals that all the signs enumerated as characteristic for oxycephaly can be recognized in them. Attention should be called here to the thinness of the vault, premature fusion of the sutures, underdeveloped accessory sinuses, shallow orbits with protruding eyes, narrow sella turcica, extremely enlarged temporal venous channels, bulging temples, high palate and crowded teeth, which are the most important features.

The similarity between oxycephaly and dysostosis multiplex becomes even more evident if one considers that true oxycephaly, according to Greig, is nearly always associated with some deformity of the extremities (syndactyly, polydactyly and contraction of fingers and toes), restricted motion of the elbow and shoulder joints, genu valgum and displacement of the patella. Poor hearing and diminished intelligence have also been recorded. With the exception of the clouded corneas, there is hardly any sign of dysostosis multiplex which is not among the complications of true oxycephaly.

There are two syndromes which are closely related to oxycephaly and dysostosis multiplex: acrocephalosyndactyly, described by Apert, and *dysostose cranio-faciale héréditaire,* described by Crouzon. The difference between them is purely morphologic. Crouzon himself said: "Dans l'ignorance où nous sommes de la lésion ou de la cause de la dysostose craniofaciale et de toutes les acrocéphalies, il semble qu'il y ait utilité de baser sur la clinique pour différencier les types, en attendant la connaissance de la lésion ou de le cause." [In our ignorance of the lesion or of the cause of the craniofacial dysostosis and of all the acrocephalias, it seems that it would be of benefit to base the differentiation of the types on the clinical aspect, while awaiting the knowledge of the lesion or of the cause.]

Acrocephalosyndactyly is, as indicated by its name, an acrocephaly associated with syndactyly. The opinion held formerly that it was not hereditary proved to be wrong (case of Romagna-Manoia, Carpenter and Wimmer). It is complicated sometimes by other bony deformities, e. g., those of the vertebrae, pelvis, sacrum and large joints, dislocation of the shoulders and the hip and anomalies of the ears and eyelids. Acrocephalosyndactyly cannot, therefore, be considered as a strictly circumscribed morbid entity; there are also borderline cases known which link it up with other syndromes (oxycephaly and dysostosis craniofacialis).

Crouzon's dysostosis craniofacialis, which was described originally as a deformity of the skull and face with protrusion of the bulbi and atrophy of the optic nerve, is due to a premature fusion of the cranial sutures. An oxycephaly, sphenocephaly or trigonocephaly develops according to the order in which the sutures fuse. Crouzon admitted, however, that there exist also mixed forms of his syndrome, in which the deformities are not confined to the skull and face (case of Lesne, Clement and Dreyfuss). Chotzen reported the interesting occurrence in one family (father and 2 sons) of signs of acrocephalosyndactyly with those of ocular hypertelorism and dysostosis craniofacialis. The deformity of the skull and other anomalies associated with these two syndromes are sufficient evidence of their relation to dysostosis multiplex.

Another syndrome which raised great interest is that of Laurence, Moon and Biedl. It is characterized by six cardinal signs: obesity, genital dystrophy, atypical "retinitis pigmentosa," mental deficiency, polydactyly and familial occurrence; one may add to these dwarfism. Both this syndrome and dysostosis multiplex consist chiefly of a congenital ocular anomaly, an endocrine disturbance and some defects of the limbs. Both are associated with dwarfism, genital hypoplasia and mental deficiency; both are inheritable, and the basal metabolic rate is reduced in both. The additional fact that impaired hearing, oxycephaly, microcephaly, brachycephaly kyphoscoliosis, genu valgum and mongolism are features commonly accompanying the Laurence-Moon-Biedl syndrome makes the analogy between the two syndromes still more striking. The chief point of difference between them lies in the nature of the ocular anomaly: While there is clouding of the corneas present in one, retinitis pigmentosa is characteristic for the other. Both are considered to be due to some developmental derangement of the eyes. The endocrine element in both is probably of hypophysial or hypothalamic origin.

A peculiar form of dwarfism was described in 1929 by Morquio. The children affected by his syndrome are disproportionate dwarfs, with a face much like that of the dysostosis multiplex group: The head is large, the neck is short, the eyes are widely spaced and the root of the nose is depressed. Kyphosis, thoracic deformities, genu valgum and umbilical hernia are usually present. The motility of the joints is restricted, but the hands and feet are flaccid; the skin is dry and coarse; colds are frequent. These patients do not improve with thyroid treatment, but, in contrast to the children with dysostosis multiplex, the intelligence is unimpaired. There are pronounced delay and disturbance in the epiphysial ossification with consequent malformations of the bones. Roentgenographically, the skull appears normal; the sella turcica is small. Judging from the pictures of Ruggles, the short neck is due to undescended shoulder blades. One cannot deny a close resemblance

between Morquio's syndrome and dysostosis multiplex; but while in the latter the skull and its nearest surroundings are predominantly affected and the peripheral lesions are of lesser degree, in Morquio's disease the reverse is the case. No clouding of the corneas has been recorded in the latter.

The classification of pleonosteosis familiaris, described by Léri under the name of *dystrophie osseuse généralisée congenitale héréditaire,* is also tentative. In many respects it resembles, and in others it differs from, dysostosis multiplex. The patients are dwarfs, with mongoloid face and defective intelligence, though without cranial deformity; they have umbilical hernia. The fingers are short and coarse and are in flexion contraction at the first interphalangeal joint; the movements of the upper and lower extremities are restricted; there is pedes vari or pedes cavi. Roentgen examination shows a broadening and thickening of the epiphyses and diaphyses with premature fusion. The features common to Léri's syndrome and dysostosis multiplex are contractions of the joints, osseous changes, defective mental state, mongoloid face and umbilical hernia. The disturbances of eye and ear are missing in this syndrome, and the skull is not deformed, yet the defective intelligence points to the possibility of a lesion of the central nervous system.

Although the inclusion of mongoloid idiocy in this group is only tentative, there are many indications that it is justified. The commonest accompanying anomalies of the skull are: brachymicrocephaly, kyphosis of the cranial basis, retarded pneumatization of the accessory sinuses, hypoplasia of the maxilla and laxity of the mandibular joint. The sella turcica varies much in size. Mental defect, epicanthus and deformed ears are often combined with opacity of the corpus vitreum (50 per cent of Ormond's cases) and congenital cataract. Some of the deformities of the periphery are: shortening and clumsiness of the fingers and toes (Comby), deformed middle phalanx of the fifth finger, syndactyly, polydactyly with laxity of the finger joints and the patella and clubfoot. The ossification of all the bones is retarded; cleft palate, umbilical and inguinal hernia are common complications. Again in mongolism, as in the previous syndromes, there is the combination of an anomalous skull, though different in shape, with malformations of the extremities, though of lesser degree.

Recently a new syndrome was described by Freeman and Sheldon under the name of craniocarpotarsal dystrophy, which warrants detailed description because it includes the presence of blebs even in postnatal life. It was observed in a boy and a girl, who, though not related, were taken for brother and sister on account of their resemblance. The boy had a remarkable history: He was a 7½ month baby of 3½ pounds

(1,533 Gm.), born by normal labor. At birth a lump was noticed at the back of the head described as "jelly-blood," which disappeared after three or four days. According to the report, ". . . the nature of this is uncertain. Its description is not that of cephalhaematoma. The lower forehead and eyebrows were occupied by a soft but prominent transverse swelling and the eyes were buried so deeply that they were hardly visible." The swellings remained as constant features of the child's face and are described as follows: "Across the lower forehead . . . is a soft subcutaneous swelling, which is shiny in reflected light and moves with the facial muscles. Similar subcutaneous bosses are present on each side of the upper forehead. . . ." The sunken eyes showed strabismus; the bridge of the nose was broad and disproportionately large in comparison with its lower part. The nasal openings were small. The cheeks were abnormally fat, rosy and shiny; the distance from the nose to the upper lip was abnormally great. The mouth and the tongue were small, and so was the whole lower part of the face below the eyes. The hands showed ulnar deviation and partial horny thickening of the skin. A bilateral talipes equinovarus completed the picture. Unusual features disclosed by the roentgenogram were: 1. The floor of the skull in the anterior fossa sloped deeply upward toward the frontal bone. 2. There was a partial failure of union between the frontal bone and the skull. 3. The facial portion of the skull was disproportionately small.

Craniocarpotarsal dystrophy presents the same combination of signs as the other eight syndromes discussed, namely, a pathologic formation of the skull and marked deformities of the upper and lower extremities. What distinguishes it from the other syndromes are the blebs in the neck and face, for which Freeman and Sheldon offered no explanation and which remained, in contrast to the other syndromes, a constant feature of the disease. In the case described the lump at the back of the head, called "jelly-blood" was not a cephalhematoma, according to the authors. This assumption was supported by the localization of the lump and by the fact that the weight of the child at birth was only 3½ pounds. The swelling of the face was probably of the same nature as that of the neck: an accumulation of cerebrospinal fluid. The unique disunion of the frontal bone with the rest of the skull was also due to an uneven distribution of subcutaneously accumulated fluid, preventing normal alinement of the two bones. The disproportions of the face were of the same origin.

The last syndrome to be discussed is that of H. H. Turner. It consists of infantilism, congenital webbed neck and cubitus valgus. It was observed in 7 women; 3 more cases were seen but not described. One of the signs is dwarfism of the proportionate pituitary type of Lorrain and Levy, associated with marked hypogenitalism. A winglike fold extends from the mastoid region almost to the acromion. The hair line

is very low on the neck. The following bone anomalies were recorded: cubitus valgus (in all 7 cases), due seemingly to an incongruity of epiphysial growth, shortening of the radius and deformity of its capitulum and defect of its distal epiphysis. Delayed union of the epiphyses, osteoporosis and decalcification of the sella turcica were also observed. The mental capacity was always normal. Treatment with extracts containing growth hormone was unsatisfactory. No opinion was expressed as to the etiologic factor, which will be discussed summarily with that of the other syndromes. So much may, however, be mentioned here: The webbed neck is certainly identical in origin or even in structure with the cutis laxa.

By comparing the ten syndromes discussed and considering their details in the literature, one comes to the conclusion that the present differentiation between the single syndromes is artificial. One encounters formes frustes of most of them; these present only a few of the classic signs. Then one sees cases which exemplify transition from one syndrome to the other or cases that combine the signs of two "classic" syndromes. One finds often single signs, split off from one or the other syndrome, occurring sporadically in the patient's ancestry. By these facts one necessarily gains the impression that one is dealing not with rigidly circumscribed morbid entities but with various manifestations of the same pathologic process.

It would serve no useful purpose to discuss separately the signs of each syndrome in the light of the bleb theory, as was done with those of dysostosis multiplex, because there is hardly one sign in the group that is not represented among those of dysostosis multiplex and that has not been dealt with. The special significance of craniocarpotarsal dystrophy was pointed out in connection with its description. Between the signs of the ten syndromes there is no difference in principle but rather one in degree, in distribution and in their combination. These differences are all compatible witih the bleb theory, which leaves great latitude for all sorts of possibilities. The damage done by the bleb depends on innumerable factors. For instance, the amount and rate of flow of the cerebrospinal fluid determine the vis a tergo and, consequently, the size, tension and distribution of the blebs. The time and extent of closure of the foramen anterius will regulate the intracranial pressure and thus the degree of involvement of the brain and skull. Bagg found that there was an association between the degree of pathologic local disturbance caused by the bleb in the embryo and the resulting final deformity of the foot. It is also to be expected that the earlier in development the limb buds are reached and distended by the blebs, the more abnormal will be the extremities in postembryonic life. The rate of reabsorption of the blebs and the tendency to bleed into the tissue have some bearing on the final consequences, which can hardly be assessed quantitatively.

The experiments of Bonnevie make it also clear why and how the same gene which is responsible for the tendency to abnormal bleb formation leads to different anomalous manifestations. According to these experiments, while the hereditary abnormality as such—the tendency to abnormal bleb formation—is caused by one main recessive gene, other genes modify the specificity of its manifestations; each of the modifying genes is responsible for specific features of the embryonic surface. There are racial differences in the molding of the embryonic surface; that is why the characteristic distribution of deformities in the American mouse tribe of Bagg and Little underwent important changes after outcrossing with two other races. For instance, outcrossing with an albino race resulted in a decrease in the percentage of deformities of the foot, while the number of anomalies of the eye has increased. Outcrossing with a piebald race had a different modifying effect. Hundreds of exact surface measurements have been made by Bonnevie. The interesting results are illustrated by the following example. In one mouse tribe the concavity of the shoulder region is greater than in others, and this factor determines the localization of the bleb in this region. The bleb in the shoulder region, on the other hand, extends easily toward the forelegs. This fact accounts for the prevalence of deformities of the foot in this special mouse tribe.

After analyzing more than 1,000 abnormal embryos, Bonnevie described five distinctly different types of deformities of the foot. In these variations I see an analogy to the different syndromes in man.

An attempt to harmonize the experimental findings and the clinical experiences should, I believe, give the following morphogenetic explanation for the syndromes discussed: Under certain unknown conditions an abundant amount of cerebrospinal fluid is produced in the medullary tube of a young embryo. If, in addition to that, the foramen anterius closes prematurely, hydrocephalus will develop with a viable pathologic or dead fetus as a result. If, on the other hand, the foramen anterius remains patent, the fluid will be drained off completely or partially toward the periphery; this drainage will act as a more or less effective safety valve. In such case there are again two possibilities. If the rates of formation and absorption of blebs balance, no peripheral deformities will necessarily develop; if the rate of formation of blebs exceeds that of absorption, an accumulation of cerebrospinal fluid will follow with major or minor damaging effect on the distal parts.

The localization of the blebs will depend on some modifying factors or genes. By regular combinations of genes some of the multiple deformities will manifest themselves as syndromes. On account of the factors mentioned, combined with the time factor, a great variety of deformities and syndromes will develop. It would be premature or even impossible to explain why in one case one, and in another case another, syndrome develops.

It has been shown that most of these syndromes are hereditary. It is understandable that besides the main tendency to pathologic escape of cerebrospinal fluid other modifying factors are also hereditary, and the combination of factors inherited determines the final form of manifestation. A thorough study of young deformed embryos, gained by abortions, and further search for signs of blebs of cerebrospinal fluid in deformed newborn children will help to confirm the "bleb theory."

From what has been said it is evident that the delimitation of the ten syndromes discussed from other clinical entities is only tentative. It is probable that more diseases will have to be included in this group in the future. For instance, dysostosis cleidocranialis, symbrachydactyly and anonychia with polydactyly are such prospective members of the group. It is possible also that one or the other of the ten syndromes will have to be dropped. Too little is known about most of these diseases for one to form a definite opinion.

The question may arise: If the bleb of cerebrospinal fluid is the cause of complicated multiple deformities, why could not single deformities develop on the same principle? It is reasonable to assume that this may well be the case: that clubfoot, congenital dislocation of the hip, Sprengel's deformity, cleft palate, spina bifida and other disunions may find a similar explanation. It may be justifiable one day to speak about a large group of diseases caused by the bleb of cerebrospinal fluid as "bleb diseases."

SUMMARY

A new theory is advanced for the morphogenesis of dysostosis multiplex. It is assumed that all signs of this disease are caused by the damaging effect of blebs of the cerebrospinal fluid which had escaped from the medullary tube into the subcutaneous tissue through the foramen anterius in early embryonic life. This theory is based partly on experiments of Bagg and Little and partly on clinical findings.

Nine other syndromes are discussed as being morphologically and morphogenetically related to dysostosis multiplex. They are considered to be different manifestations of the same etiologic factor. The name of "bleb diseases" is proposed for this group. It is suggested that the bleb of cerebrospinal fluid plays an important part in the etiology of single and multiple deformities.

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# NONDIABETIC GLYCOSURIA IN CHILDREN

## REPORT OF NINE CASES

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AND
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Although the diagnosis of nondiabetic glycosuria is not infrequently made, to the practicing physician the label is still not an altogether happy one. Given repeated credible reports of glycosuria, the burden of proof still rests heavily on the physician who says "this is not diabetes." Nevertheless, the recent survey of Marble, Joslin and associates [1] bears out the correctness of the diagnosis and demonstrates that the condition is usually benign.

It is especially difficult to rule out diabetes in children. Since the variations of blood sugar in the child are so great, normal readings are not always a guarantee of normal sugar metabolism: On a moderately restricted diet a child with mild diabetes may have a normal fasting or an occasionally normal postprandial reading. Also, since a neglected diabetic condition in childhood may deteriorate so rapidly, the responsibility is great for detecting the disease as early as possible.

But it is equally unfortunate in children to view too gravely a repeated glycosuria of dubious significance. Children find even mild dietary restraints burdensome. Parents probably worry more over the possibility of diabetes developing in their children than in themselves. Furthermore, if the glycosuria is really not diabetic, it now appears that the chances are even less that diabetes will subsequently develop in children than in adults.[1]

A series of cases is here presented which gives support to an optimistic outlook with regard to the prognosis of children with atypical glycosuria.

Between 1923 and 1938 some 50 children passed through the pediatric ward of Stanford University School of Medicine with a diagnosis of possible diabetes mellitus. The glycosuria of 9 of these children was either considered nondiabetic or called diabetic with definite reservations

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This work was aided by the grant of an anonymous donor.

From the Departments of Medicine and Pediatrics, Stanford University School of Medicine.

1. Marble, A.; Joslin, E. P.; Dublin, L. I., and Marks, H. H.: Studies in Diabetes Mellitus: VII. Non-Diabetic Glycosuria, Am. J. M. Sc. **197**:533-556 (April) 1939.

*Clinical Data for Nine Children with Nondiabetic Glycosuria*

| | | Original Status | | | | | Interval | | Present Status | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient | Diabetes in Family | Age, Years | Occasion of Investigation | Glycosuria Observed* | Dextrose Tolerance | Original Diagnosis | Elapsed Years | Restriction of Carbohydrate | Age, Years | Glycosuria Observed | Dextrose Tolerance | Present Diagnosis |
| C. P. | 0 | 2.0 | Acute febrile illness | ++ | Decrease | Diabetes mellitus | 7.0 | Moderate at first | 9.0 | 0 | Normal | Normal |
| B. L. | 0 | 2.7 | Acute Vincents angina | + | ..... | Unclassified glycosuria | 6.4 | 0 | 9.1 | 0 | Normal | Normal |
| V. M. | 0 | 3.7 | Acute asthma | + | ..... | Unclassified glycosuria | 6.9 | 0 | 10.6 | ++ | Normal | Unclassified glycosuria |
| K. W. | Paternal grandmother | 6.4 | Preparation for tonsillectomy | ++ | ..... | Diabetes mellitus | 6.9 | Moderate at first | 13.3 | 0 | Normal | Normal |
| J. K. | Aunt; father | 6.5 | Preparation for tonsillectomy; failure to gain weight | + | Normal | Diabetes mellitus | 6.1 | Moderate at first | 12.6 | 0 | Normal | Normal |
| M. M. | Father | 8.6 | Glycosuria found repeatedly by father | 0 | Decrease | Diabetes potential | 11.5 | Moderate at first | 20.1 | 0 | Normal | Normal |
| N. G. | 0 | 9.2 | Preparation for repair of cleft palate; enuresis; pruritus; poor healing of wound | +++ | Normal | Diabetes mellitus | 6.0 | Moderate | 15.2 | ++ | Normal | Unclassified glycosuria |
| J. M. | Paternal uncle; paternal grandfather; great-grandfather | 9.7 | Glycosuria found recurrently since age of 6; enuresis | + | Decrease | Diabetes mellitus | 2.2 | 0 | 11.9 | 0 | Decrease | Hyperglycemia after ingestion of dextrose |
| C. H. | 0 | 10.3 | Glycosuria since age of 7 | 0 | Normal | Diabetes mellitus | 5.9 | 0 | 16.2 | 0 | Normal | Normal |

* The degree of glycosuria is indicated as follows: +, trace or mild; ++, moderate; +++, marked.

on the part of the staff. In the spring of 1939, from two to eleven years after the original diagnoses were made, it was possible to recheck every one of these 9 patients. Today not 1 of them is diabetic. All are boys.

The accompanying table gives the essential clinical data. Three boys were below the age of 4 years when first studied in the ward.

Individual growth curves and end points of the records of height and weight are shown in charts 1 and 2. Except for 1 boy who was overweight at the start, the group enjoyed normal development throughout.

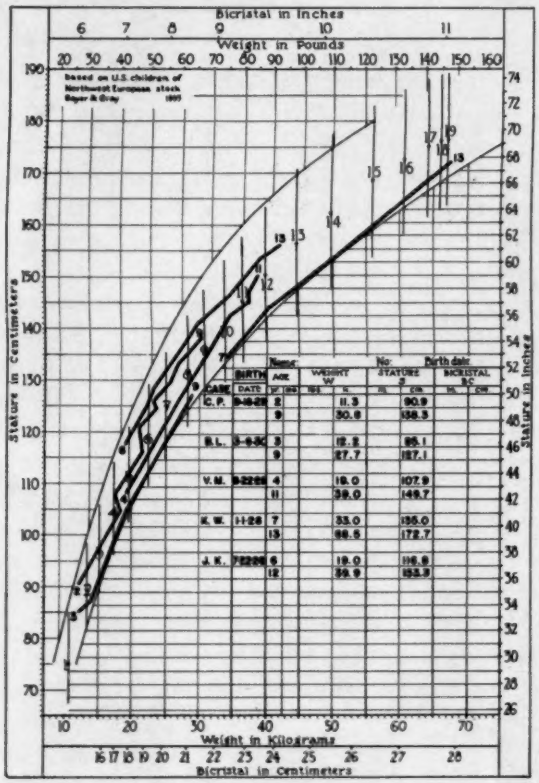


Chart 1.—Curves for 5 boys with nondiabetic glycosuria showing growth in height and weight.

The original diagnoses were: diabetes mellitus, 5; potential diabetes, 2; unclassified glycosuria, 2. Criteria conform to those in common practice. Urinary sugars were determined by Benedict's qualitative test. Tests for the venous blood sugars were done by the method of Folin and Wu.

Chart 3 is a composite of the six original dextrose tolerance tests on record. Every point represents one reading in a test. The average values at each time interval ($x$) are connected by straight lines. When

all individual connecting lines are drawn, the picture is too confusing. However, the curves of the 2 children for whom high readings were obtained are separately indicated. They show that the abnormal blood sugars occurred between low fasting and terminal determinations. Even when these high readings are included in the averages, the mean curve gives a fair sketch of the facts: The responses were atypical and equivocal but not definitely pathognomonic of diabetes.

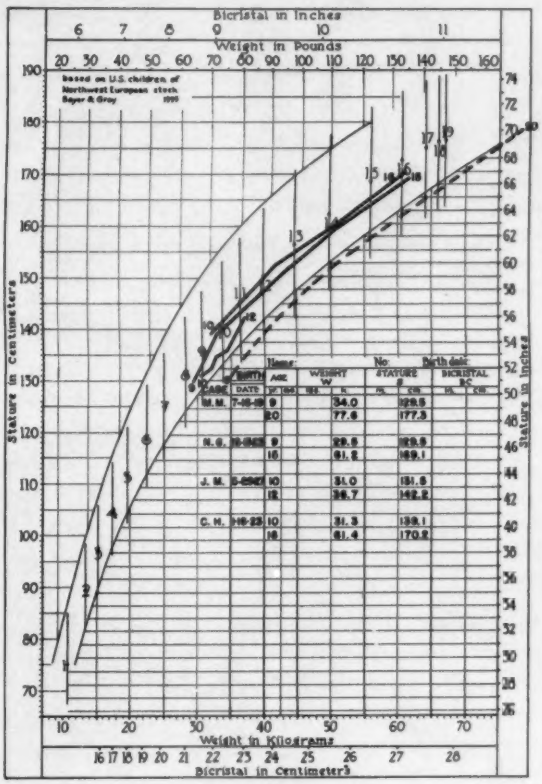


Chart 2.—Curves for 4 boys with nondiabetic glycosuria showing growth in height and weight.

The original diagnoses rested, as always, on clinical judgment. Suggestive symptoms and the existence of diabetes elsewhere in the family were important factors coloring the decisions; also, the fact that some of the children were sent in from out of town for diagnosis only and would not be subject to observation in the clinic had some influence. It is interesting that in the father of 1 patient, J. K., diabetes developed as recently as August 1938. Viewed in retrospect, some of the classifications would, no doubt, be changed today. It should be repeated that

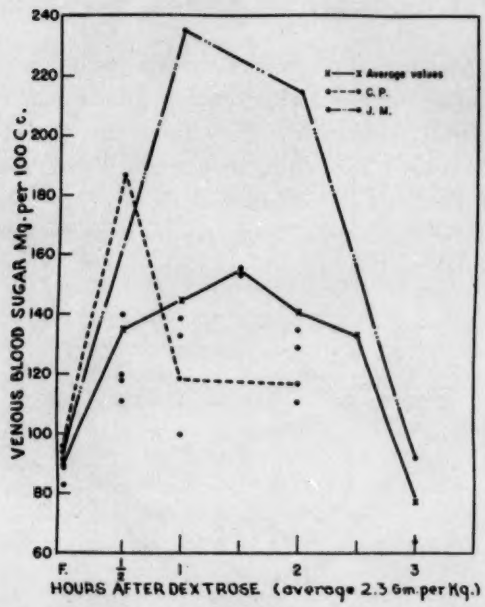


Chart 3.—Curves showing results of the first dextrose tolerance tests of 6 children with nondiabetic glycosuria. Curve $x—x$ represents the average values for all the readings at each time interval. The other curves represent the readings of the two individual tests which showed the highest values.

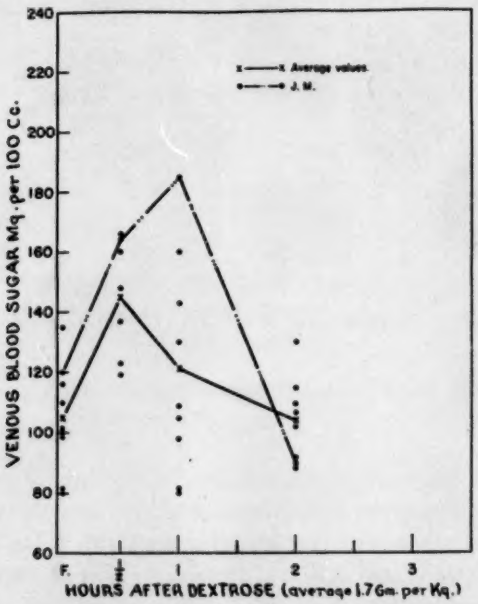


Chart 4.—Curves showing results of the dextrose tolerance tests performed during recheck of the children. Curve $x—x$ represents average values for all 9 boys; the other curve plots the readings for J. M., who had a disproportionately high level of blood sugar after ingestion of dextrose.

the diagnoses of diabetes mellitus were seriously questioned at the time they were made, and it was for this reason that the children were called for reexamination.

Since the 1939 recheck, the present diagnoses are: normal, 6; unclassified glycosuria, 2; hyperglycemia after ingestion of dextrose, 1. Because so much time has elapsed, these verdicts can be pronounced with relative confidence. Only 1 child, N. G., maintained a moderately curtailed intake of carbohydrate and sweets. The others either early relaxed their restrictions or were on a free diet throughout. The fact that they have not grown worse suggests that their sugar metabolism could not have been seriously deranged.

Chart 4 shows the essentially normal character of the recent dextrose tolerance tests. J. M. again responded with a disproportionately high level of blood sugar after ingestion of dextrose; there was no corresponding glycosuria. His curve is again separately indicated by dotted lines. A few of the latter tests were done by the La Motte method. Glycosuria occurred in only 2 instances, as indicated in the table.

Prior to the dextrose tolerance tests, 7 of the 9 children were in the ward for two days on their customary diet. Readings were taken of the blood sugar before and between meals and at bedtime. These daily curves were all normal. Glycosuria was never found during these preliminary days, although all single specimens of urine were tested.

The ultimate diagnoses cannot, of course, be foretold. According to Marble's report, the important factors with regard to the cases of these 9 children are that all of them were below 20 years of age when first seen, 8 are of average or less than average weight and 4 have a positive history of diabetes in the family. This combination of variables suggests that not more than 10 per cent, or 1 child, will eventually become diabetic. Long-continued watchfulness is certainly advisable with all of them and especially with those from diabetic families. But their prospects of escaping diabetes are good, so that it seems proper to give these boys considerable encouragement.

# REGIONAL OBSTRUCTIVE PULMONARY EMPHYSEMA IN INFANTS AND IN CHILDREN

## EMPHYSEMATOUS CAVITIES AND THEIR SIMILARITY TO NECROTIC CAVITIES, CONGENITAL PULMONARY CYSTS AND LOCULATED PNEUMOTHORAX

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Pulmonary cavitations appear roentgenographically as areas of rarefaction with diminished lung markings, usually bounded by annular shadows of increased density. If cavities are partially filled with fluid, air-fluid levels are present that shift with changes in position of the patient. In the early days of roentgenology it was believed that such areas were caused only by pulmonary destruction, and they were diagnosed as either pulmonary abscess or tuberculous cavitation.[1] Later it was demonstrated that such shadows could also originate in the pleura and might represent the loculation of air, with or without fluid, in the pleural space.[2] When large pulmonary cavities have been present in roentgenograms of young infants, congenital cysts of the lung have usually been invoked to explain their formation.[3] More recently, substantial evidence has appeared which indicates that localized obstructive emphysema is an important factor in the production of cavernous lesions in the lungs.

Roentgenographically I have seen many large and small pulmonary cavities containing air alone or air and fluid develop in the course of

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From the Department of Pediatrics, Columbia University College of Physicians and Surgeons, and the Babies' Hospital.

Read in summary at the meeting of the Society for Pediatric Research, Skytop, Pa., April 27, 1939.

1. Brown, P. K.: Annular Shadows: Are They Cavities or Spontaneous Pneumothoraces? Am. J. Roentgenol. **10**:443, 1923. Evans, W. A.: The Significance of Annular Shadows, ibid. **6**:510, 1919.

2. Fishberg, M.: Localized and Interlobar Pneumothorax Complicating Pulmonary Tuberculosis, Arch. Int. Med. **20**:739 (Nov.) 1917. Sampson, H. L.; Heise, F. N., and Brown, L.: A Study of Pulmonary and Pleural Annular Shadows, Am. Rev. Tuberc. **2**:664, 1919. Anderson, J. B., Jr.: The Nature and Differentiation of Pleural Annular Shadows, Am. J. Roentgenol. **12**:438, 1924.

3. (*a*) Schenck, S. G.: Congenital Cystic Disease of the Lungs: A Clinicopathological Study, Am. J. Roentgenol. **35**:604, 1936. (*b*) Peirce, C. B., and Dirkse, P. R.: Pulmonary Pneumatocele (Localized Alveolar or Lobular Ectasia): Certain Considerations in Cystic Disease of the Lung, Radiology **28**:651, 1937.

infections of the respiratory tract in infants and children. It has not been possible to make a direct correlation of these lesions with the actual anatomic changes in the lung, because the benign clinical course and the complete recovery of all patients have not permitted direct examination, either during surgical exposure or at necropsy. In serial roentgenograms, however, the size and shape of these cavities have fluctuated so rapidly that destruction of pulmonary tissue seems an improbable explanation of their production. Their rapid dilatation and contraction, sometimes followed by reexpansion and recontraction, furnish strong presumptive evidence that inflationary forces were more important than destructive agents in their genesis. Lacking absolute anatomic proof, I believe that it is highly probable that these cavities were caused by localized pulmonary emphysema distal to transient bronchial obstruction of the check valve type.

A description of the clinical courses of these patients, with their roentgenographic features, seems appropriate at this time for several reasons. Emphysematous pulmonary cavitation has received relatively little attention in the pediatric literature. Air-fluid levels in pulmonary cavities are usually considered diagnostic of pulmonary destruction,[4] and I wish to emphasize that inflammatory exudate in an emphysematous cavity may produce air-fluid levels that cannot be differentiated roentgenographically from the air-fluid levels seen in necrotic cavities containing necrotic fluid. Finally I wish to direct attention to the benign course of emphysematous cavities, since all of these patients recovered satisfactorily without surgical intervention.

This report is based on a roentgenographic study of 20 patients seen over a period of eight years in whose lungs, in the course of infections of the respiratory tract, air pockets larger than 2 cm. in diameter developed. The following 7 selected cases illustrate the clinical and roentgenographic features in: (*a*) 3 cases in which emphysematous cavities with shifting air-fluid levels developed (cases, 1, 2 and 3), (*b*) 1 case in which an emphysematous cavity appeared early in an attack of lobar pneumonia (case 4), (*c*) 1 case in which an emphysematous cavity appeared after tonsillectomy (case 5) and (*d*) 2 cases in which large emphysematous pulmonary cavities appeared in young infants, 1 with air-fluid levels (case 6) and 1 without air-fluid levels (case 7), producing a roentgenographic picture similar to that which has been described as produced by congenital cysts of the lung.

## REPORT OF CASES

CASE 1.—*Single large emphysematous cavity with air-fluid levels appearing late in pneumonia and with reinflation following involution of the pneumonia.*

4. Neuhof, H., and Touroff, A. S. W.: Acute (Non-Putrid) Abscess of the Lung, Surgery **4**:728, 1938.

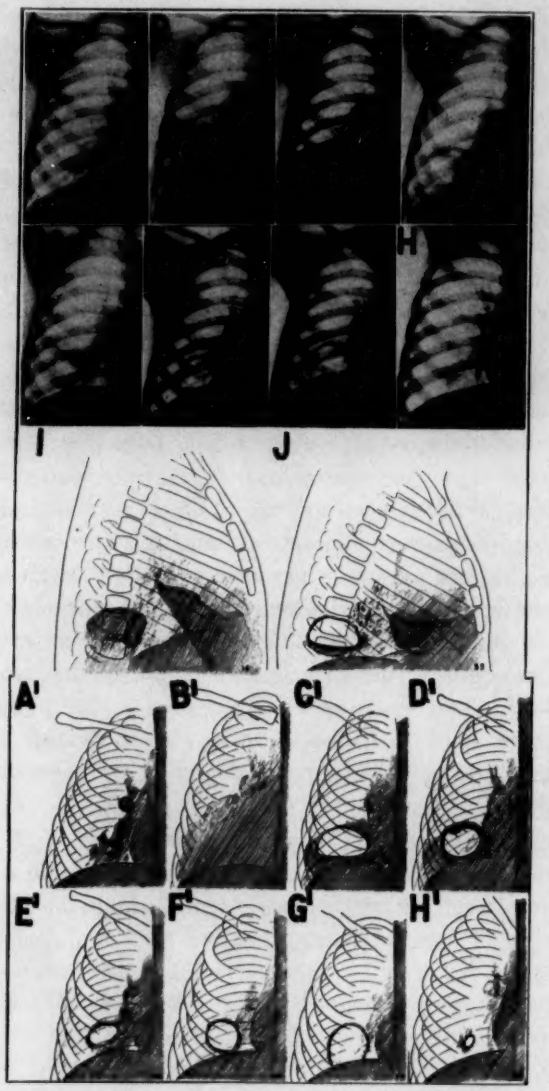


Fig. 1 (case 1).—Roentgenograms and drawings showing a single large emphysematous cavity with air-fluid levels. *A*, roentgenogram made on the eighth day of the illness, showing pneumonic consolidation in the right lung. *B*, roentgenogram made on the fourteenth day, showing extension of the pneumonic consolidation. *C*, roentgenogram made on the thirty-fifth day, showing a large cavity in the area of consolidation with a horizontal air-fluid level which shifted with changes in the position of the patient. *D*, roentgenogram made on the thirty-seventh day, showing beginning clearing of the pneumonic exudate, reduction in size and change in the shape of the cavity and disappearance of the intracavitary fluid. *E*, roentgenogram made on the fortieth day, showing further reduction in the size of the cavity with clearing of pneumonia. *F*, roentgenogram made on the

*(Legend continued on next page)*

M. H., a girl 3 years of age, was admitted to the hospital seven days after the onset of cough, fever and nausea. Resonance was impaired in the lower part of the right side of the thorax, and fine rales and bronchial breathing were heard in the same area. Pneumococci of an undetermined type were present in the nasopharynx on several examinations. Two blood cultures were sterile. The blood count made on the patient's admission showed 14.5 Gm. of hemoglobin per hundred cubic centimeters and 8,700 leukocytes per cubic millimeter, of which polymorphonuclears made up 52 per cent, lymphocytes 44 per cent, monocytes 2 per cent and eosinophils 2 per cent. The Mantoux test (0.1 mg.) was negative.

The patient remained in the hospital for forty-four days, from the eighth to the fifty-second day of her disease. Fever continued until the thirty-fifth day, when it subsided suddenly and permanently. The physical signs in the lower part of the right side of the thorax disappeared at approximately the same time. The patient coughed occasionally throughout the febrile period but brought up no purulent sputum, and the odor of the breath was not foul. She remained asymptomatic, and the physical findings were normal during a follow-up period of eighteen months. At no time during or following the illness were there any clinical signs of pulmonary cavitation.

Serial roentgenograms of the thorax are shown in figure 1. In *A* and *B*, taken on the eighth and fourteenth days of the disease, pneumonic consolidation is seen in the lower and middle lobes of the right lung. (A lateral projection made on the fourteenth day is shown in figure 1 *I*.) In *C*, taken on the thirty-fifth day, a large cavity 37 by 21 by 40 mm., surrounded by annular shadows and containing a horizontal air-fluid level, is present in the pneumonic area in the lower lobe of the right lung (lateral projection, figure 1 *J*). The air-fluid level was shown to shift with a change in the position of the patient roentgenoscopically and in films which are not reproduced. In *D*, taken on the thirty-seventh day, the cavity has changed its shape, decreased in size and lost most of its fluid. In *E*, taken on the fortieth day, the cavity is shrunken to 20 by 11 mm., and the consolidation has practically cleared. In *F*, taken on the forty-eighth day, practically all of the pneumonic consolidation has disappeared, and notwithstanding, the cavity has increased to 28 by 27 mm. without a reaccumulation of fluid. In *G*, taken on the fifty-seventh day, the cavity has continued to increase in size to 30 by 33 mm. and again appears to be dry. In *H*, taken on the eighty-fifth day, there is a second reduction in the size of the cavity, so that it is barely visible. In subsequent films taken over a period of eighteen months no abnormalities were visible in the thorax. In *A'* to *H'* the pulmonary changes are shown semidiagrammatically.

The following features in this case make it probable that the cavity was caused by localized distention (regional emphysema) rather than

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forty-eighth day, showing reexpansion of the cavity without recurrence of pneumonitis or air-fluid level. *G*, roentgenogram made on the fifty-seventh day, showing continued reinflation of the cavity. *H*, roentgenogram made on the eighty-fifth day, showing marked contraction of the cavity. *I*, right lateral projection of the thorax on the fourteenth day (dorsoventral projection, *B*) showing pneumonia in the lower and middle lobes of the right lung (semidiagrammatic). *J*, right lateral projection of the thorax on the thirty-fifth day (dorsoventral projection, *D*) showing a cavity in the pneumonic area in the lower lobe of the right lung. *A'* to *H'*, semidiagrammatic representations of *A* to *H*.

by destruction of tissue (benign abscess): the development of this cavity at a time when the patient was asymptomatic, the complete lack of constitutional symptoms when the cavity was enlarging on the forty-fifth and fifty-seventh days, fluctuation in size and shape of the cavity and the secondary dilatation of the cavity on the forty-fifth and fifty-seventh days without the simultaneous reaccumulation of fluid within it.

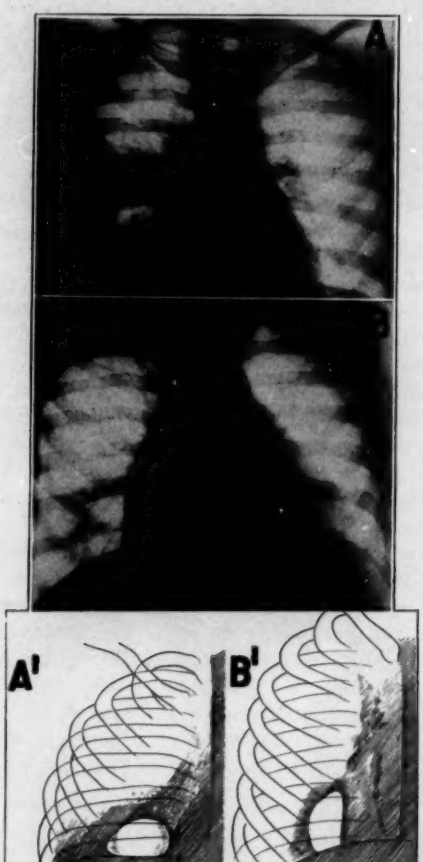


Fig. 2 (case 2).—Roentgenograms and drawings showing a large emphysematous cavity in a patient with lobar pneumonia with a shift in the air-fluid levels with a change of position from the erect to the horizontal. *A*, roentgenogram made with the patient in the erect position, showing a transverse air-fluid level. *B*, roentgenogram made with the patient in the recumbent position with the left side dependent, showing a shift of the air-fluid level to a plane parallel with the long axis of the body. *A'* and *B'*, semidiagrammatic representations of *A* and *B*.

CASE 2.—*A large emphysematous cavity showing a shift in the horizontal air-fluid level with changes in position of the patient.*

R. C., a boy 9 years of age, was admitted to the hospital on the fifth day of an acute infection of the respiratory tract, with a history of cough, fever,

vomiting and abdominal pain. Physical examination revealed that he was acutely ill with fever, paroxysmal cough and dyspnea. He was obese, weighing 53 Kg., and had the distribution of fat and small genitalia suggestive of Fröhlich's syndrome. The respiratory amplitude of the right side of the thorax was reduced, and fine rales and a pleural rub were heard posteriorly at the base of the right lung. The lower part of the right side of the abdomen was tender, and the right rectus muscle was hypertonic. Digital examination of the rectum gave negative results. The blood contained 18,000 leukocytes per cubic millimeter, of which 76 per cent were polymorphonuclears, 15 per cent lymphocytes, 4 per cent monocytes, 4 per cent eosinophils and 1 per cent myeloblasts.

The fever, cough and physical signs in the lower part of the right side of the thorax persisted from the fifth to the twelfth day of the disease, when they subsided, and they did not recur. Postural drainage was instituted because of the cavity seen in the roentgenograms taken on admission and occasionally yielded a small amount of viscous pus, which contained micrococci (Micrococcus catarrhalis), pneumococci and staphylococci but was free of spirochetes. The patient remained in the hospital until thirty days after onset of the illness and was asymptomatic after the twelfth day. He was then followed as an outpatient for two years and during this period remained free from respiratory complaints.

Roentgenographic examination in dorsoventral and lateral projections disclosed a triangular shadow of increased density in the posteroinferior medial portion of the lower lobe of the right lung. Within this area of consolidation there was a cavity of air density, 32 by 28 mm., which contained a horizontal air-fluid level. Figure 2 shows this lesion on the twelfth day of the disease, when the cavity had increased to 44 by 27 mm. *A* in figure 2 demonstrates the transverse horizontal fluid-air level when the patient was in the erect position, and *B* shows the shift of the air-fluid level to a plane parallel with the long axis of the body with the patient in a horizontal position with the left side dependent. In later films, not reproduced, taken on the twenty-third day, the consolidation and the cavity were barely visible, and on the fifty-fourth day the right lung appeared to be normal.

CASE 3.—*Multiple, transient, benign, fluctuating, emphysematous cavities, with and without air-fluid levels.*

In M. N., a boy, an infection of the upper respiratory tract developed at the age of 4 months; he had frequent recurrences thereafter. At 16 months the right tympanic membrane was incised. This was followed by simple mastoidectomy. The tonsils and adenoids were removed three weeks later. During the next year he had purulent discharge from both ears intermittently, and at 30 months bilateral radical mastoidectomy was performed. The lungs showed no pathologic signs at this time. Three weeks later rhinitis, laryngitis and tracheal cough developed, rales were heard in both lungs and impairment of resonance and bronchovascular breathing were present in the lower part of the left side of the thorax posteriorly. The tuberculin test was negative (0.1 mg.).

The child was admitted to the hospital four weeks after the second mastoidectomy because of fever and profuse nasal discharge of eight days' duration. Posteriorly at the base of the left lung resonance was impaired, the breath sounds were suppressed and throughout both lungs rales were heard. There was no amphoric breathing, and the odor of the breath was not unusual. Streptococcus haemolyticus and Staphylococcus aureus were present in throat cultures, but no bacteria grew in blood cultures. The clinical findings suggested bronchopneumonia, with probable pleuritis at the base of the left lung.

Roentgenograms taken at this time, eight days after the onset of cough and fever, are shown in *A*, figure 3. In the lower lobe of the left lung there was a cavity 20 by 10 mm., surrounded by a dense thick wall and with an air-fluid level which shifted with a change in the position of the patient. In the upper lobe of the right lung there were several smaller cavities without fluid content.

Bronchoscopy was done one week later, and much pus was found on both sides of the bronchial tree. The roentgenographic findings at this time, fifteen

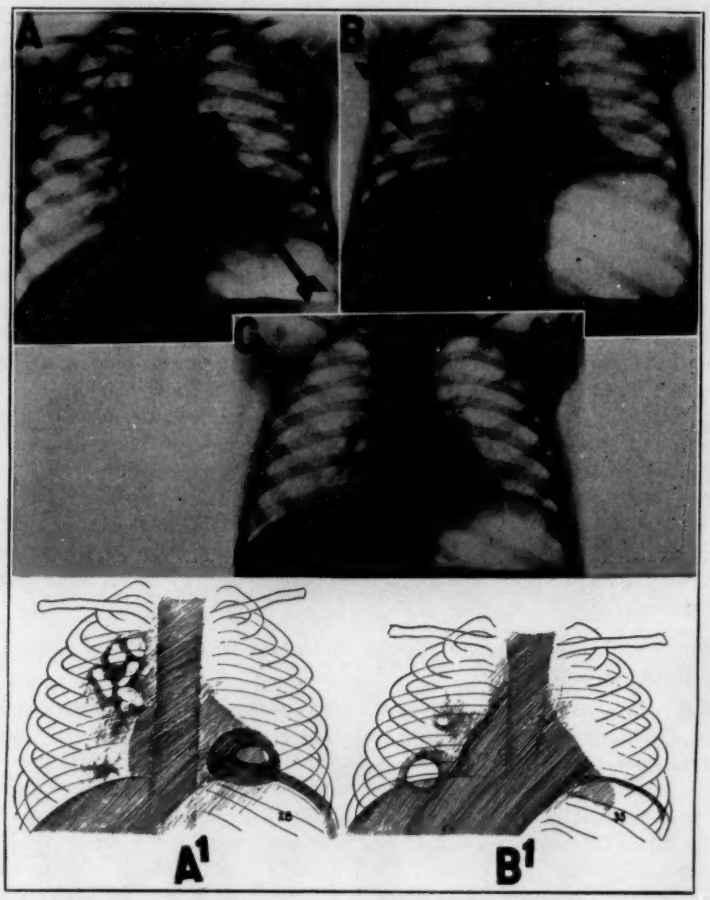


Fig. 3 (case 3).—Roentgenograms and drawing showing multiple, transient, benign, fluctuating, emphysematous cavities with and without fluid levels. *A*, roentgenogram made on the eighth day of the illness, showing a large cavity with a horizontal fluid level at the base of the left lung and multiple dry cavities in the upper lobe of the right lung. *B*, roentgenogram made on the fifteenth day of the illness. The large cavity in the left lung, as well as some of the smaller cavities in the upper lobe of the right lung, has disappeared. In the lower lobe of the right lung a new large cavity has developed since the examination seven days previously. *C*, roentgenogram made nine weeks after the onset of fever. No cavities are visible. *A'* and *B'*, semidiagrammatic representations of *A* and *B*.

days after the onset of fever and cough, are shown in *B*, figure 3. The cavity previously present in the left lung had practically disappeared, while a new cavity, 20 by 15 mm., was present in the lower lobe of the right lung. In the upper lobe of the right lung the multiple small cavities were reduced in number and had changed their pattern. *C* shows the disappearance of all pulmonary lesions at the time of discharge from the hospital, nine weeks after the onset of cough and fever.

Bronchoscopy was repeated three weeks after the onset of the fever, and the amount of purulent exudate visible in the bronchial tree was much reduced as compared with the first bronchoscopic examination two weeks before. The septic fever persisted for three weeks after the onset, when it subsided and the physical signs in the chest disappeared. The patient remained in the hospital for six additional weeks, and there was no recurrence of symptoms indicative of relapse in the pulmonary infection. The mastoidectomy wounds healed satisfactorily. The patient has now been under observation for nine years, and the lungs have appeared normal in repeated clinical and roentgenographic examinations.

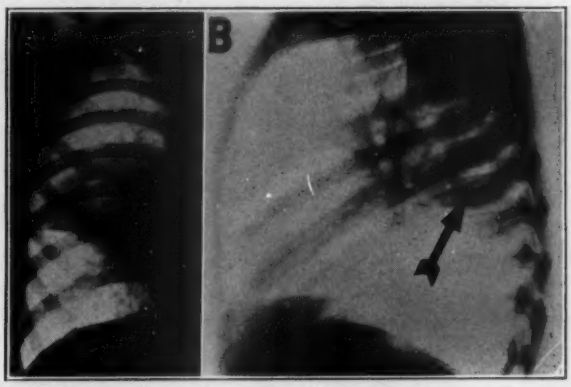


Fig. 4 (case 4).—Roentgenograms showing a large emphysematous cavity which developed during the first four days of the disease in the lung of a patient with lobar pneumonia. *A*, dorsoventral projection, showing pneumonic consolidation in the perihilar region of the right lung, which contains a large cavity. *B*, lateral projection showing the posterior position of the lesion in the apex of the lower lobe of the right lung.

In view of the rapid disappearance of the fluid-containing cavity in the lower lobe of the left lung, with the synchronous development of a cavity in the lower lobe of the right lung and the clearing of the multiple cavities in the upper lobe of the right lung, it is probable that the cavitations in these lungs resulted from hyperinflation of segments of the lung behind multiple, transient, bronchial obstructions rather than from multiple necrotic destruction of lung tissue, that is, from obstructive emphysema rather than from abscess formation.

CASE 4.—*A single, large cavity, without fluid, early in lobar pneumonia.*

R. B., a boy 8½ years of age, had had mild signs of an infection of the upper respiratory tract for two weeks and cough and high fever for four days when first seen. Examination on admission to the hospital disclosed impairment

of resonance, bronchial breath sounds and rales over the subscapular region of the right side of the thorax. In the blood there were 22,000 leukocytes per cubic millimeter, 80 per cent of which were polymorphonuclears, 17 per cent lymphocytes and 3 per cent monocytes. The Mantoux test (0.1 mg.) was negative. Pneumococci, which could not be typed, predominated in the sputum. Fever continued for fourteen days after the onset, and when it subsided the physical signs also disappeared. The patient has remained well during the subsequent two years.

Roentgenograms made four days after the onset of fever (fig. 4, *A*) demonof the consolidation there was a sharply circumscribed area of air density, 20 by 22 mm. With the patient in the right lateral position (fig. 4, *B*) it could be strated a patch of consolidation in the right lung. Within the heavy shadow clearly seen that this cavity lay within the pneumonic lung, posteriorly, in the apex of the lower lobe of the right lung. In roentgenograms taken seven days later the size of the cavity was so much reduced that it was hardly visible, although the area of consolidation had persisted with little change. The patient was reexamined roentgenographically one year later, and the right lung appeared normal.

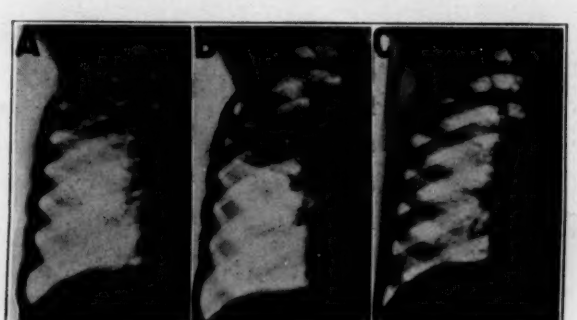

Fig. 5 (case 5).—Roentgenograms showing an emphysematous cavity which developed after tonsillectomy. *A*, roentgenogram made on the fourth day after the onset of fever. There is a large area of consolidation containing the cavity, in the upper lobe of the right lung. *B*, roentgenogram made on the eighth day, showing considerable expansion of the cavity. *C*, roentgenogram made on the twenty-third day; the cavity has decreased in size, and the surrounding pneumonitis has almost disappeared.

This case is of special interest because this large pulmonary cavity was already present on the fourth day of the disease. It may have developed on the first, second or third day. The benign clinical course of the infection and the absence of physical signs of cavitation are noteworthy in the presence of a cavity of this magnitude.

CASE 5.—*A large emphysematous cavity following tonsillectomy.*

S. C., a Negro girl 11 years of age, had been under observation since the fifth year of life for sickle cell anemia. The tonsils and adenoids had been removed thirteen days before admission, and ten days later fever and cough had developed. Fever of 104 F., pallor and a short systolic cardiac bruit were found on physical examination. There were no pathologic signs in the lungs, and the spleen was not palpable. The reaction to the Mantoux test with 2 mg. of tuber-

culin was negative. The blood contained 5.8 Gm. of hemoglobin per hundred cubic centimeters, 2,000,000 erythrocytes per cubic millimeter, 1,100,000 thrombocytes and 21,000 leukocytes, 91 per cent of which were polymorphonuclears, 7 per cent lymphocytes, 1 per cent monocytes and 1 per cent eosinophils. Many sickle cells were present in blood smears.

With the exception of fever, the patient was practically asymptomatic during her hospital residence of forty days. At no time were the physical signs indicative of pulmonary abscess. The fever subsided ten days after the onset. Bronchoscopy was done four days later, and a small amount of pus was seen in the right bronchial tree after coughing. Postural drainage yielded small amounts of pus for several days following bronchoscopy. No tubercle bacilli could be found in 8 specimens of the material obtained by postural drainage. The patient has now been under observation for seven years since the tonsillectomy, and there have been no respiratory complaints.

Roentgenograms made on the fourth, eighth and twenty-third days after the onset of fever are shown in figure 5. In *A*, taken on the fourth day, there is a diffuse increase in density in the upper lobe of the right lung, in which there is a sharply circumscribed cavity 25 by 15 mm. In *B*, taken on the eighth day, the cavity has increased to 29 by 25 mm. In *C*, taken on the twenty-third day, the increase in density of the upper lobe of the right lung has largely disappeared and the cavity is reduced to 18 by 18 mm. On the thirty-first day (film not reproduced) the cavity was of approximately the same size, and the annular shadow surrounding it was faint. A roentgenogram made three years later disclosed no pathologic changes in the thorax.

Post-tonsillectomy abscess and tuberculous cavitation were both given much consideration in the differential diagnoses. The latter can be satisfactorily excluded because of the negative tuberculin test, the negative examination of the sputum for tubercle bacilli and the rapid clearing of both the cavity and the surrounding pulmonary exudate. There may have been some pulmonary destruction in the formation of this cavity, and necrosis cannot be excluded as a partial factor. I believe it must also be conceded that obstructive emphysema may have been a factor. The ballooned-out contour of the cavity and the expansion of the cavity on the eighth day (fig. 5 *B*) suggest that an inflationary factor was present.

CASE 6.—*Large emphysematous cavities with air-fluid levels in an infant 4 months of age, resembling congenital cysts of the lung.*

J. B., a girl, was asymptomatic until 3 months of age, when a "head cold with cough," fever and vomiting appeared. The fever had persisted for three weeks and the vomiting for ten days when she was first examined. On one occasion reddish brown discoloration of the material vomited had suggested blood to the parents.

The patient was well nourished and did not appear to be acutely ill. The temperature on admission was 99.6 F. The left tympanic membrane was congested, and the mucous membranes of the nose and throat were moderately injected. There was some impairment of resonance in the upper part of the right side of the thorax, but the breath sounds in this region were not abnormal. The Mantoux and the Kline tests were negative.

The blood contained 5,500,000 erythrocytes per cubic millimeter and 10.7 Gm. of hemoglobin per hundred cubic centimeters. There were 30,000 leukocytes per cubic millimeter, of which 65 per cent were polymorphonuclears, 26 per cent

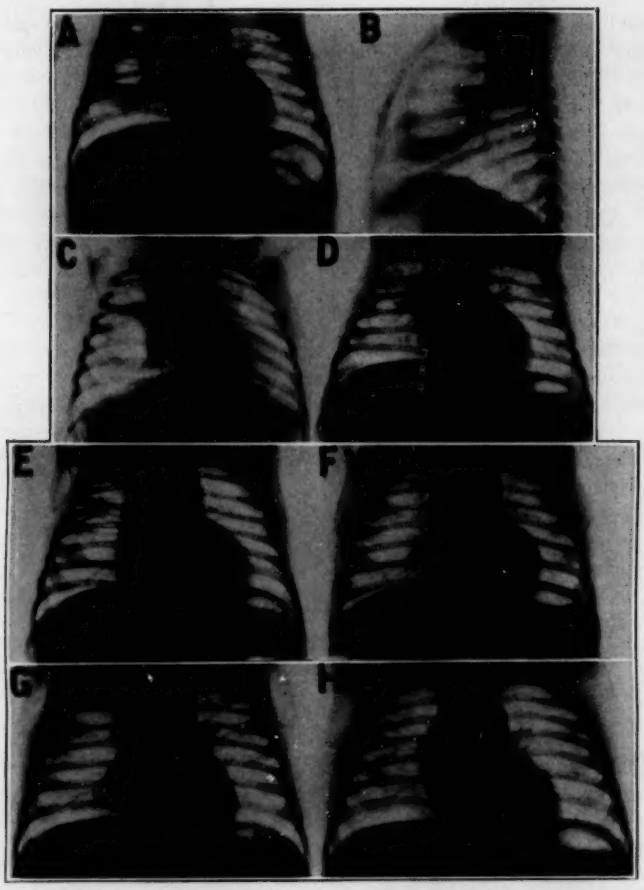


Fig. 6 (case 6).—Roentgenograms showing a large, emphysematous cavity with air-fluid levels resembling congenital cyst of the lung in an infant 4 months of age. *A*, roentgenogram made on the day of admission (erect position, frontal plane projection), showing two large cavities with transverse fluid levels in the consolidated upper lobe of the right lung. The larger cavity measured 19 by 22 mm. *B*, roentgenogram made on the day of admission (erect position, lateral plane projection), showing large cavities surrounded by consolidated lung. *C*, roentgenogram made on the day of admission (horizontal position with left side down), showing a shift of the air-fluid level to the long axis of the body as compared with the transverse air-fluid level in *A*. *D*, roentgenogram made sixteen days after admission, showing clearing of the consolidation and contraction of the cavities. The largest cavity now measured 10 by 6 mm. *E*, roentgenogram made thirty days after admission, showing continued clearing of the consolidation but with reexpansion of the cavities (20 by 23 mm.). There is no reaccumulation of fluid within the cavity. *F*, roentgenogram made fifty-one days after admission, showing progressive expansion of the cavity (44 by 30 mm.). *G*, roentgenogram made three months after admission, showing persistence of the large cavity (51 by 33 mm.). *H*, roentgenogram made five months after admission; the cavitation has completely disappeared, leaving linear arcuate shadows, probably sequelae of the surrounding annular shadows present in the previous films.

lymphocytes and 9 per cent monocytes. The sedimentation rate of the erythrocytes was 65 mm. in one hour. Pneumococcus, type 17, was identified in cultures from the nasopharynx. A blood culture yielded no growth.

During the first week in the hospital there were frequent paroxysms of coughing, associated with cyanosis and considerable mucoid sputum. A low grade fever continued throughout the first week, after which the patient was asymptomatic during a hospital residence of thirty-six days. She has now been under observation at home for five months and has remained well.

Roentgenographic examinations of the thorax were made on admission and frequently thereafter over a period of five months. The findings are shown and described in detail in the legends under figure 6. The association of these large cavities with consolidation of the remainder of the upper lobe of the right lung, shortly after the onset of an infection of the upper respiratory tract in an infant who had previously been asymptomatic, the fluctuations in the size of the cavities, their reexpansion without recurrence of the consolidation and reaccumulation of fluid within the cavities (fig. 6 *A, D, E* and *F*) and their complete disappearance are all difficult to explain on the basis of either congenital cystic disease of the lung or pulmonary abscess. These occurrences are satisfactorily explained on the basis of localized pulmonary emphysema distal to multiple check valve bronchial obstructions. Features of special interest in this patient are the persistence of large cavities over a period of more than three months and their ultimately benign course.

CASE 7.—*Two large high pressure emphysematous cavities in an infant 5 months of age, resembling congenital cysts of the lung.*

G. P., a boy, was admitted when 5 months of age. An intermittent nasal discharge had been present in the early weeks of life. In the third month he had had cough, fever and nasal discharge for approximately two weeks from which he had recovered satisfactorily, and he was then well until two days before admission. At this time he became feverish, a discharge from the nose developed and the next day he exhibited alarming respiratory distress and pallor.

On examination he was cyanotic and dyspneic and had frequent short hacking paroxysms of coughing. The left side of the thorax was enlarged, hyperresonant and practically immobile. The breath sounds in the lower two thirds of the left side of the chest were suppressed, and occasional fine rales were heard. There were no abnormal signs in the right lung, and the heart appeared to be displaced to the right. Roentgenoscopic examination revealed two large cavities of air density in the left side of the thorax. Barium sulfate was given by mouth, and no communication between the channels of the gastrointestinal tract and the pulmonary cavities could be demonstrated.

By direct puncture through the thoracic wall gas was aspirated from the lower cavity for chemical analysis. Its oxygen content was found to be between 10 and 15 per cent, which is within the normal range for alveolar air. At a second similar puncture the pressure within the pulmonary cavity was found to be considerably higher than atmospheric. In view of the fact that the child was crying during the procedure, this increase in intrapulmonary pressure is not surprising. However, it was observed that the pressure fluctuated but little in the different phases of the respiratory cycle. Three hundred cubic centimeters of gas was aspirated rapidly without producing any change in the patient's clinical

condition or, indeed, any roentgenographically detectable diminution in the size of the cystic areas. These occurrences indicated that a large amount of gas was entrapped in this cavity under high pressure and that the cavity refilled almost immediately after aspiration, probably from the regional bronchi. The hyperinflation of this part of the lung and the rapid refilling after aspiration can be most satisfactorily explained by a check valve bronchial obstruction, which blocked the outflow of air from the tributary segments of the lung during expiration and permitted its entrance during inspiration. This type of obstruction can be produced by plugs of thick mucus which form during inflammation of the upper respiratory tract. It is not necessary to assume that a congenital defect of the lung or bronchi was also present in this patient.

The fever subsided after the first twenty-four hours, with only slight relapses. The dyspnea, cyanosis and cough, however, persisted, and the roentgenographic

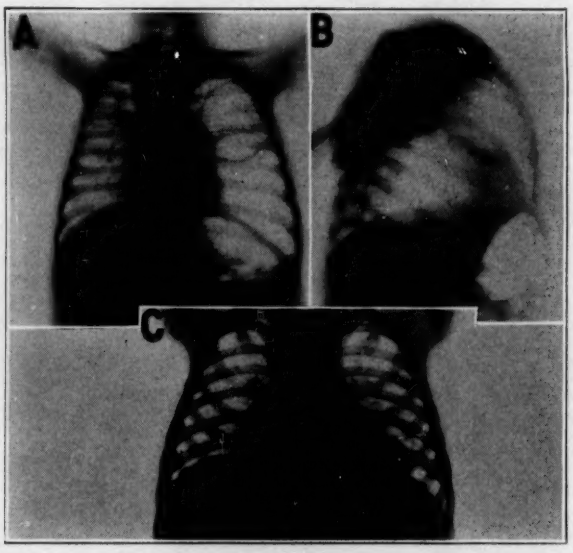


Fig. 7 (case 7).—Roentgenograms showing two large high pressure emphysematous cavities resembling congenital cysts of the lung in an infant 5 months of age. *A,* roentgenogram showing two ballooned-out cavities in the left lung on the eleventh day. *B,* lateral projection of *A*. *C,* roentgenogram showing normal findings seventeen months later.

appearance was unchanged during twenty-six days of hospital residence. Roentgenograms made on the eleventh day are shown in figure 7, *A* and *B*. Two large ballooned-out cavities, sharply circumscribed with annular shadows, filled the greater portion of the left side of the thorax. The upper cavity measured 45 by 37 by 41 mm. and the lower cavity 75 by 54 by 63 mm. The heart was displaced to the right, and the left leaf of the diaphragm was depressed.

Although the cavities were still present unchanged on the twenty-sixth day, the patient was taken home by the parents. They stated that the dyspnea, cyanosis and cough disappeared abruptly a few days after the patient left the hospital, and that he remained asymptomatic thereafter. He was not examined again until seventeen months later, at which time the clinical and roentgen findings were normal (fig. 7, *C*).

COMMENT

In the differential diagnosis the following lesions were considered as possible causes of the cavities seen in the roentgenograms: (1) acute pulmonary abscess, (2) aputrid pulmonary necrosis, (3) tuberculous cavitation, (4) loculated pneumothorax or pyopneumothorax, (5) congenital cysts of the lung and (6) regional obstructive emphysema.

Destructive changes, such as benign pulmonary abscess, cannot be eliminated entirely as partial factors in cavity formation, but they appear to have played a minor or even negligible role in these patients, for the reasons stated in detail in the case reports (cases 1, 3, 5 and 6 particularly). The most impressive evidence that these cavities were not caused by necrosis is seen in cases 1 and 6, in which, after partial contraction, the cavities reexpanded without the recurrence of inflammatory changes in the contiguous lung and without the reaccumulation of fluid within the cavities and when there were no constitutional signs of infection. In case 3 the rapid shift in the pattern of multiple cavities during a single week is not consistent with pulmonary destruction. Fluid levels in pulmonary cavities are usually considered pathognomonic of pulmonary abscess.[4] But if my interpretation of the pathogenesis of these lesions is correct, then the shifting air-fluid levels seen in the emphysematous cavities in these patients (cases 1, 2, 3 and 6) indicate that inflammatory fluid exudates in emphysematous cavities produce shifting air-fluid levels similar to those caused by necrotic fluid in necrotic cavities. In a consideration of the time factor alone it seems unlikely that the cavities seen in cases 2, 4 and 5 were caused by inflammatory destruction of pulmonary tissue on the fourth, fifth and third days, respectively, of the pulmonary infections.

The relatively rare condition of aputrid pulmonary necrosis has been offered by Kessel[5] in explanation of the benign cavities which appeared in roentgenograms of adults with lobar pneumonia, usually at the time of resolution. He expressed the belief that these benign cavities were caused by pulmonary infarction following thrombosis of a pulmonary vessel. In my cases the same objections hold for aputrid necrosis that have already been discussed under pulmonary abscess.

Cavitation of primary pulmonary tuberculosis is practically excluded in all of these patients by the absence of cutaneous sensitivity to tuberculin. Also, in primary tuberculosis the involution both of large exudates and of destructive changes is rarely, if ever, as rapid as in these patients. In case 5 bacilli could not be demonstrated in 8 specimens of sputum. It seems probable, however, that some of the cavities seen in tuberculosis and looked on as destructive may be produced by

5. Kessel, L.: Clinical Aspect of Aputrid Pulmonary Necrosis, Arch. Int. Med. **45**:401 (March) 1930.

localized emphysema.[6] Miller[7] and Friedman[8] have both recorded cases in which large emphysematous bullae demonstrated at necropsy in tuberculous lungs had been mistaken roentgenographically for destructive tuberculous cavities.

Loculated pneumothorax and pyopneumothorax can be most clearly differentiated from pulmonary cavitation by diagnostic pneumothorax. Artificial pneumothorax was not induced for diagnosis in these patients because the benign clinical course contraindicated any potentially dangerous procedure. Matheja[9] and Peirce and Dirkse,[5b] however, in similar cases demonstrated with artificial pneumothorax that the cavitations lay within the pulmonary tissue. Study of my patients in lateral, oblique and dorsoventral projection shows strips of lung surrounding the peripheries of the cavities (figs. 1, 4, 6 and 7 particularly) and demonstrates satisfactorily that the cavities are situated in the lungs and not in the pleural spaces.

The question of congenital cystic disease of the lung should be raised in the differential diagnosis perhaps only in cases 6 and 7, in young infants 4 and 5 months of age, who had large pulmonary cavities. The most convincing evidence that the cavities were not congenital cysts and that they were not caused by congenital malformation is their complete disappearance shown in later examinations. In case 6 there is associated extensive consolidation of the upper lobe of the right lung, which is not found in congenital cystic diseases. In case 7 the high intracavitary pressure and the communication with the bronchi, demonstrated by aspiration, can be explained only by check valve bronchial obstruction. Since these cavernous changes were already present in both patients when the first roentgenograms were made in the fourth and fifth months of life, it is not known whether they were present prior to this time. There is no reason, however, to believe that they were present in the first weeks of life, because the infants were asymptomatic until infection and fever developed many weeks later. All of the clinical and roentgenographic data in these cases can be explained on the basis of loculated pulmonary emphysema distal to bronchial obstruction which developed during infections of the respiratory tract in the fourth and fifth months of life. Few, if any, of the data support an assumption that the cavities were congenital cysts or that congenital malformation played a part in their formation.

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6. Spivek, M. L.: Obstructive Pulmonary Emphysema Due to Partial Obstruction of Bronchi by Tuberculous Lesions, Am. J. Dis. Child. **51**:69 (Jan.) 1936.

7. Miller, W. S.: A Tuberculous Lung in Which a Large Emphysematous Bulla Was Mistaken for a Cavity, Am. Rev. Tuberc. **28**:359, 1933.

8. Friedman, E.: Emphysematous Blebs and Bullae, Am. J. Roentgenol. **35**: 324, 1936.

9. Matheja, W.: Fehldiagnosen bei Emphysemblasen der kindlichen Lunge, Ztschr. f. Kinderh. **60**:236, 1938.

Peirce and Dirkse [3b] have described 2 cases similar to case 7. One of their cases is of special interest because normal lungs were demonstrated roentgenographically several weeks before a large cavity developed during the resolution of lobar pneumonia. These authors expressed doubt of the validity of the diagnosis of "congenital cystic disease" in many cases reported as such, and they pointed out the rarity of authentic cases of cysts in the lungs of fetuses and of newly born infants and also the rarity of cysts containing fluid as compared with the frequency of cysts containing air at all ages. They expressed the belief that it is improbable that congenital cysts containing fluid would rupture so frequently and become aerated and consider it more probable that the large cavities containing air seen in young infants are caused by localized emphysema. They prefer that these emphysematous cavities be called pneumatoceles or localized lobular ectasia. Recently two reports of localized emphysema, erroneously diagnosed as congenital cysts of the lung, have appeared in the French literature.[10] The histopathology and pathogenesis of true congenital cysts of the lung have been described in detail by Anspach and Wolman.[11]

The importance of localized obstructive emphysema in the production of pulmonary cavities surrounded by annular shadows was first pointed out by Laurell [12] in 1925. In 1926 and 1927 Miller [13] published his careful anatomic studies of pulmonary blebs and bullae; he suspected that these loculated emphysematous lesions might cause annular shadows in roentgenograms. According to Miller, bullae are formed by the distention of the alveoli themselves, and the larger bullae are the result of rupture of the alveolar walls and fusion of the dilated spaces. Blebs are formed by the escape of air into the interstitial tissues of the lung and localization in the areolar connective tissue of the pleura. The air in the bulla is intra-alveolar, and this lesion has also been called vesicular emphysema, alveolar emphysema and alveolar ectasia. The air in the bleb lies outside the alveoli in the interstitial tissues of the lung, and this lesion is known also as interstitial emphysema. It is probably not

10. Brulé, M.; Hillemand, P.; Delarue, J., and Gaube, R.: Emphysème pulmonaire à grosses bulles, simulant des kystes congénitaux du poumon, Bull. et mém. Soc. méd. d. hôp. de Paris **53**:478, 1937. Lereboullet, P.; Lelong, M., and Bernard, J.: Emphysème à grosse bulle solitaire, simultant un grand kyste congénital du poumon, chez un nourrisson de quatre mois (emphysème ampullaire), ibid. **53**:506, 1937.

11. Anspach, W. E., and Wolman, I. J.: Large Pulmonary Air Cysts of Infancy, Surg., Gynec. & Obst. **56**:635, 1933.

12. Laurell, H.: A Few Words on Annular Shadows in the Lungs, Acta radiol. **4**:634, 1925.

13. Miller, W. S.: (*a*) A Study of the Human Pleura Pulmonalis: Its Relation to Blebs and Bullae of Emphysema, Am. J. Roentgenol. **15**:399, 1926; (*b*) A Further Study of Emphysematous Blebs, ibid. **18**:42, 1927.

possible to differentiate pulmonary blebs and bullae with any degree of certainty roentgenographically. The wide strips of lung between the cavities and the pleura in cases 1, 4 and 6 suggest that the cavities were caused by bullous emphysema rather than by interstitial emphysema. It is unlikely that the rapidly disappearing fluid levels seen in cases 1, 2, 3 and 6 would be found in pulmonary blebs (interstitial emphysema). In case 7 the almost instantaneous refilling of the cavity after aspiration of 300 cc. of air is more consistent with alveolar emphysema than interstitial emphysema. It is possible for bullae and blebs to be present simultaneously, and interstitial emphysema may follow bullous emphysema as a sequel to the rupture of the overdistended alveolar walls and extravasation of air into the interstitial tissues.

Arnell [14] made the first authentic correlation of the anatomic and roentgenographic observations in 1927, when he described an asthmatic patient, 38 years of age, who had annular shadows around pulmonary air pockets in roentgenograms and whose lung at necropsy showed both bullae and blebs. Doub [15] in 1928 reported the first American cases in which necropsy showed pulmonary blebs and bullae in areas corresponding to cavernous annular shadows in roentgenograms. In 1929 Laurell [16] demonstrated experimentally by inflating with air the tracheas of excised calves' lungs that the margins of emphysematous blebs and bullae cast ring shadows in roentgenograms, and he concluded that many such lesions had been mistaken for pneumothoraxes and pleural rings. Microscopically he found that the ring shadows were caused by "belts of compression atelectasis" in the alveoli contiguous to the borders of emphysematous air pockets. In their studies of whole sections of lungs in 1929, McNeil, Macgregor and Alexander [17] found that blebs and bullae were a conspicuous feature of bronchopneumonia and that bullae were present occasionally in infants and children with lobar pneumonia.

More recently, in 1936 and 1937, the roentgenographic features of localized pulmonary emphysema have been described by Friedman [8] and by Snow and Cassasa.[18] The latter authors have expressed the belief that obstructive emphysema is a major etiologic factor in severe dyspnea

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14. Arnell, S.: Annular Shadows in the Lungs Caused by Sub-Pleural Emphysema, Acta radiol. **8**:252, 1927.

15. Doub, H. P.: Sub-Pleural Emphysema as a Causative Factor in the Formation of Annular Shadows, Am. J. Roentgenol. **20**:6, 1928.

16. Laurell, H.: Ein Beitrag zur Deutung der sogenannten Ringschatten in den Lungen, Acta radiol. **10**:72, 1929.

17. McNeil, C.; Macgregor, A. R., and Alexander, W. A.: Studies of Pneumonia in Childhood, Arch. Dis. Childhood **4**:83, 1929.

18. Snow, W., and Cassasa, C. S. B.: Obstructive Emphysema and Atelectasis in Acute Respiratory Disease of Infants, Am. J. Roentgenol. **37**:217, 1937.

and cyanosis in infantile pneumonias. Toniolo [19] in 1936 discussed the differential diagnosis of the findings in roentgenograms caused by pulmonary cavities and reported a case in which the pulmonary cavity seen in a roentgenogram proved to be subpleural emphysema at necropsy. The similarity of regional emphysematous cavitation to benign pulmonary abscess was not reported in the pediatric literature until 1938, when Matheja [9] described the roentgenographic changes associated with pneumonia in 3 patients, 7 weeks, 6 months and 7 years of age. Benjamin and Childe [20] have recently presented this subject for the first time (November 1939) in the American pediatric literature. They found localized bullous emphysema associated with pneumonia in 19 patients, ranging from 3 months to 13 years of age. Their data in several cases which they describe are similar to those in some of my cases. They found air-fluid levels in the emphysematous spaces in 5 patients. In 1 patient a cavity persisted after ten months of observation. Both their experience and mine indicate that emphysematous cavitation of the lung is not an infrequent complication of infections of the respiratory tract in infants and children, since they encountered 19 cases over a period of six years and I have seen 20 cases during a period of eight years.

Castex and his associates [21] have visualized pulmonary blebs and bullae with a pleuroscope and have correlated the anatomic, roentgenographic and pleuroscopic findings. They found that the pleuroscopic image was similar to the lesion found at necropsy and was situated in the portion of the lung where a cavity was seen in the roentgenogram.

The causal mechanism in obstructive emphysema has become well known through the bronchoscopic studies of Jackson and his colleagues.[22] They have pointed out that thick, viscid, inflammatory exudate, as well as foreign bodies, can cause bronchial obstruction. If the bronchial obstruction is complete (of the stop valve type), regional atelectasis of the lung results. If, however, the bronchial obstruction is of the check valve type, which permits the inflow of air during inspiration but obstructs the escape of air during expiration, a cumulative alveolar distention occurs in the segment of the lung distal to the obstruction. All

19. Toniolo, G.: Possibilità ed importanza delle immagini pseudocavernose (studio clinico ed anatomopathologico), Radiol. med. **23**:927, 1936.

20. Benjamin, B., and Childe, A. E.: Localized Bullous Emphysema Associated with Pneumonia in Children, J. Pediat. **15**:621, 1939.

21. Castex, M.; Mazzei, E., and Vaccarezza, O.: Anatomie, radiologie et pleuroscopie des bulles sous-pleurales: Role de l'effort dans leur formation et rupture, Arch. méd.-chir. de l'app. respir. **12**:345, 1937.

22. (*a*) Jackson, C.; Spencer, W. H., and Manges, W. F.: The Diagnosis and Localization of Non-Opaque Foreign Bodies in the Bronchi, Am. J. Roentgenol. **7**:277, 1920. (*b*) Jackson, C.: The Mechanism of Physical Signs with Especial Reference to Foreign Bodies in the Bronchi, Am. J. M. Sc. **165**:313, 1923; (*c*) Bronchoscopy: Past, Present and Future, New England J. Med. **199**:759, 1928.

of the patients reported on here had infections of the upper respiratory tract, and I believe that inflammatory exudate produced check valve bronchial obstruction and regional emphysema.

It should be emphasized that in normal respiration the bronchi dilate during inspiration and contract during expiration and that this normal generalized expiratory contraction of the bronchial tree predisposes to focal, increased, check valve obstruction whenever thick bronchial exudate may be present in the bronchial tree. Jackson [22a] observed bronchoscopically that the bronchi are not rigid tubes like gas pipes but that they fluctuate rhythmically during the respiratory cycle, expanding and lengthening during inspiration and contracting and shortening during expiration. Heinbecker [23] observed this same expansile-contractile bronchial phenomenon in normal respiration roentgenographically after the instillation of iodized poppyseed oil, and he found that the bronchi and the bronchioles are largest at the end of full inspiration and smallest at the end of full expiration. Hudson and Jarre [24] confirmed Heinbecker's observation by taking serial films of the lungs with a "Cin-Ex camera" after the instillation of iodized poppyseed oil into the bronchial tree. They found the same inspiratory dilatation and expiratory contraction of the bronchi, and in some instances at the peak of expiration the walls of the bronchi were so close that they seemed to touch each other. It is interesting that Watson-Williams [25] in 1903 speculated that it was probable that bronchial muscles dilated and contracted rhythmically during inspiration and expiration like the alae nasi and the vocal cords.

Coryllos and Birnbaum,[26] after extensive experimental and clinical investigations, came to the conclusion that atelectasis caused by bronchial obstruction is the primary factor in the pathogenesis of lobar pneumonia, but they also pointed out that emphysema rather than atelectasis occurs when the bronchial obstruction is incomplete. The interesting experimental studies of Van Allen and Lindskog [27] on the collateral respiration of the lung and obstructive emphysema in dogs deserve consideration. They were able to produce lobar emphysema by placing check valve obstructions in the primary bronchi, but no emphysema resulted when

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23. Heinbecker, P.: A Method for the Demonstration of Calibre Changes in the Bronchi in Normal Respiration, J. Clin. Investigation **4**:459, 1927.

24. Hudson, W. A., and Jarre, H. A.: Functional Studies of the Tracheo-Bronchial Tree, with Aid of Cin-Ex Camera, Brit. J. Radiol. **2**:523, 1929.

25. Watson-Williams, cited by Hudson and Jarre.[24]

26. Coryllos, P. N., and Birnbaum, G. L.: Bronchial Obstruction: Its Relation to Atelectasis, Bronchopneumonia and Lobar Pneumonia; Roentgenographic, Experimental and Clinical Study, Am. J. Roentgenol. **22**:401, 1929.

27. Van Allen, C. M.: Obstructive Pulmonary Emphysema and Collateral Respiration, Surg., Gynec. & Obst. **55**:303, 1932. Lindskog, G. E., and Van Allen, C. M.: The Aerodynamics of Bronchial Obstruction, Arch. Surg. **24**:204 (Feb.) 1932.

check valve obstructions were placed distal to the primary bronchi. They explained this difference in the effect of valvular bronchial obstruction in the primary bronchi and in more distal bronchi by the fact that there is a collateral circulation of air between the lobules of any one lobe but not between different lobes, and that this collateral circulation removes the excessive air in any segment of a lobe as rapidly as it accumulates. This collateral circulation of the different portions of a lobe is made possible by abundant communicating passages between lobules (probably the alveolar pores of Kohn) and also, perhaps, by diffusion of air through the alveolar walls. In a footnote they commented that it is conceivable that obstructive emphysema might occur in a single lobule but that this would be possible only under conditions which interfere with collateral respiration between lobules. I believe it probable that inflammatory reaction in the lung might well obstruct these communicating channels and thus interfere with intralobular collateral pulmonary circulation and make possible partial or fractional lobar emphysema. Moreover, in human beings lobular emphysema in inflamed lungs has been demonstrated at necropsy several times (Arnell,[14] Miller,[13] Doub[15] and Laurell[16]).

## SUMMARY

The clinical and roentgenographic observations on 7 infants and children in whom pulmonary cavities developed during infections of the respiratory tract are reported.

The differential diagnosis of pulmonary cavitation is considered, and it is concluded that in these cases the clinical and serial roentgenographic features are consistent with regional obstructive emphysema and are not consistent with pulmonary abscess or congenital cystic disease of the lung.

The question is raised whether air-fluid levels in pulmonary cavities are pathognomonic of pulmonary abscess, and it is suggested that in these cases inflammatory fluid exudate in emphysematous cavities caused shifting air-fluid levels similar to those produced by necrotic fluid in necrotic cavities.

The pertinent literature is reviewed dealing with the morbid anatomy, the roentgenographic signs and the bronchoscopic observations in regional emphysema and with its causal mechanism, incomplete bronchial obstruction.

# ESTIMATION OF VITAMIN D IN BLOOD SERUM

## II. LEVEL OF VITAMIN D IN HUMAN BLOOD SERUMS

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AND
HELEN E. MABON, M.D.
CINCINNATI

In a previous communication a method for the estimation of vitamin D in blood serum was described.[1] It was shown that the level of vitamin D in the serum of animals can be raised by a single administration of a large dose of viosterol and that the surplus of vitamin D disappears from the serum within a few weeks. In addition, the results of a number of estimations in serums of children and adults were reported.

In the present study we wish to supplement the data concerning the level of vitamin D in human serums. It seems desirable to know not only the average value of the vitamin D in human serums but the variations which may be expected. Since those variations, which may be due to physiologic fluctuations or to the limitations of the method, are rather large, a knowledge of the fluctuations observed in the blood of normal human beings is necessary for the evaluation of results with abnormal serums. It will be shown in subsequent communications that the variations found under various abnormal conditions are far beyond the limits of normal variations.

The present report is based on 608 line tests obtained by assaying 155 samples of human blood serum over a period of several years.

One hundred and eleven samples of blood were obtained from white and 44 from Negro children and adults. Eighty-eight samples were from children under 14 years of age, 4 from adolescents between 14 and 18 years and 63 from adults between 24 and 76 years. All the adults tested were white. Serums of infants were not included in this study.

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From the Children's Hospital Research Foundation and the Department of Pediatrics, University of Cincinnati.

1. Warkany, J.: Estimation of Vitamin D in Blood Serum, Am. J. Dis. Child. **52**:831 (Oct.) 1936.

In this first communication the headings of the last two columns of tables 1 to 3 and 6 to 12 should read "Vitamin D Content of Rabbit's Serum per 100 Cc." instead of "Vitamin D Content of Rat's Serum per 100 Cc." The inscription below the abscissa of chart 2 should read "1.0 cc. of viosterol (1,000,000 U. S. P. units) instead of 0.1 cc. viosterol (100,000 U. S. P. units)." On page 833, line 13 should read "Wheat gluten, 20 per cent," instead of "Wheat gluten, 30 per cent."

There were excluded from this analysis the serums of persons who were seriously ill or who had received treatment by artificial ultraviolet irradiation or with vitamin D, as cod liver oil or in any other form, within the three months preceding the test.

## METHODS

Biologic methods must be used for the estimation of vitamin D in body fluids and tissues. Several years ago, when this study was begun, it was thought that the biologic estimation would soon be replaced by a simple and accurate physical or chemical determination. It is apparent, however, that for some time to come this hope will not be realized, since a variety of compounds, differing in physical and chemical properties, have proved effective against rickets.[2] It appears improbable, therefore, that any specific physical or chemical test will replace the highly sensitive biologic test in the near future.

Obviously, the methods generally used for assaying vitamin D in substances such as cod liver oil and milk had to be modified to a certain extent when applied to human blood serum, which is not available in sufficient amounts to allow a satisfactory assay of every sample by such methods. A single value by itself may be unsatisfactory, but a considerable number of assays will furnish satisfactory average figures.

Blood taken from a vein in the arm was allowed to stand for one-half hour to one hour at room temperature, then centrifuged and the serum pipetted off. Amounts[3] of 1.5, 2, 2.5, 3, 3.5, 4 (and sometimes 5) cc. respectively were each mixed with about 40 Gm. of the Steenbock and Black diet[4] no. 2965. After being air-dried, these mixtures were finely pulverized in a porcelain mortar and put into glass bottles.

The rats were fed the rachitogenic diet for twenty-one days. They were then fed the same diet plus serum, added as described, for eight days. For rats that consumed more than 5 Gm. of their diet daily, these mixtures were supplemented with varying amounts of rachitogenic diet. Thus it was possible to distribute the intake of serum over the whole eight day period. After ten days the line tests[5] were performed in the usual manner and rated as follows: 0, no deposit of silver between the zone of cartilage and the intermediate zone; +, a small

2. Bills, C. E.: Chemistry of Vitamin D, J. A. M. A. **110**:2150 (June 25) 1938.

3. The total phosphorus content of human blood serum amounts to approximately 12 mg. per hundred cubic centimeters. By feeding 5 cc. of serum, the maximum amount administered in our assays, an additional amount of approximately 0.6 mg. of phosphorus was added to a rat's diet over the eight day period. This quantity does not disturb the calcium: phosphorus ratio of the diet and has not been considered a factor in the assays.

4. Steenbock, H., and Black, A.: Fat-Souble Vitamins: Induction of Growth-Promoting and Calcifying Properties in Fats and Their Unsaponifiable Constituents by Exposure to Light, J. Biol. Chem. **64**:263 (June) 1925.

5. McCollum, E. V.; Simmonds, N.; Shipley, P. G., and Park, E. A.: Studies on Experimental Rickets: Delicate Biological Test for Calcium-Depositing Substances, J. Biol. Chem. **51**:41 (March) 1922.

deposit of silver or an incomplete line between the two zones; ++, a complete and thin line; +++, a heavy line, and ++++, calcification extensive enough to reach the osseous part of the shaft.

When these experiments were begun, the Steenbock unit of vitamin D was still widely used. It was defined as the total amount of vitamin D which would produce a narrow line of calcium deposit in the rachitic metaphyses of the long bones of standard rachitic rats in a period of ten days. Accordingly, we attempted to ascertain the minimum amount of serum required to produce ++ healing in rachitic rats. At the present time, the Steenbock unit has been replaced by the international, or U. S. P., unit. At first, 1 Steenbock unit was considered equivalent to 2.7 international, or U. S. P. XI, units.[6] However, Russell and Taylor[7] considered 1 Steenbock unit equivalent to 3.2 U. S. P. units for their animal colony. Haman and Steenbock,[8] in a study on energy equivalents of vitamin D units, stated that a comparison of the energy equivalents of the Steenbock unit and the international unit "as obtained in independently executed series of assays, and direct comparison of the biological potency of the International Standard Preparation with a preparation produced by a measured amount of monochromatic ultraviolet revealed that one Steenbock unit of Vitamin-D is equivalent to 3.33 International units." Since it is possible that different equivalents can be found for the Steenbock unit under varying experimental conditions, it was thought necessary to ascertain the equivalent under the conditions of our laboratory. In the course of one year various amounts of reference oil (1 Gm. containing 95 U. S. P. units of vitamin D) were fed by pipet to 105 rats These amounts corresponded to 20.7, 24.2, 27.7, 31.2, 34.7 and 38.2 mg. of oil for the eight day period. After ten days line tests were made. For each amount of reference oil a certain percentage of line tests resulted in ++ healing (or more). This percentage increased with the amount of oil administered, and it was possible to construct a curve which indicated the percentage of ++ line tests obtained from each amount of reference oil. It was found that 35.1 mg. of reference oil (an amount which corresponded to 3.33 U. S. P. units of vitamin D) produced ++ healing in 66 per cent of the line tests. In this study a factor of 3.3 was used, therefore, to convert Steenbock units into U. S. P. units.

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6. Steenbock, H.; Kletzien, S. W. F., and Halpin, J. G.: (*a*) Reaction of Chicken to Irradiated Ergosterol and Irradiated Yeast as Contrasted with Natural Vitamin D of Fish Liver Oils, J. Biol. Chem. **97**:249 (July) 1932; (*b*) Recent Developments in Pharmacopeial Vitamin Standardization, J. A. M. A. **102**:1877 (June 2) 1934.

7. Russell, W. C., and Taylor, M. W.: Relation Between Vitamin A and D Intake by the Hen and the Output in Eggs, J. Nutrition **10**:613 (Dec.) 1935.

8. Haman, R. W., and Steenbock, H.: Energy Equivalents of Vitamin D Units, Indust. & Engin. Chem. (Anal. Ed.) **8**:291, 1936.

As a rule, increased healing in a series of rats could be expected when the amount of serum fed was increased from 1.5 cc. to 4 cc., the increment being 0.5 cc. The minimum amount which would produce ++ healing was considered the curative dose, i.e., 1 Steenbock unit.

Figure 1 illustrates the results of such an assay. Two cubic centimeters of serum did not produce any calcification between cartilage and the intermediate zone, but 2.5 cc. produced beginning healing rated as

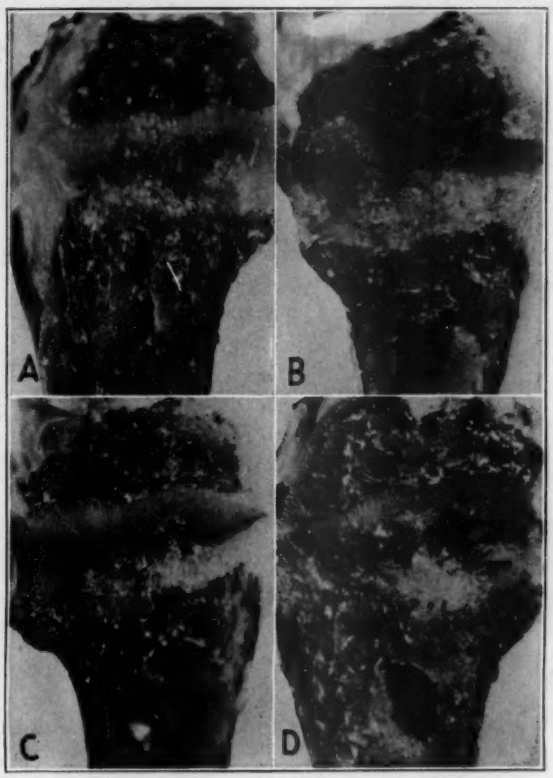


Fig. 1.—Line tests obtained with the administration of increasing amounts of human blood serum. *A* shows negative healing with 2 cc. of serum; *B* shows + healing with 2.5 cc.; *C* shows ++ healing with 3 cc., and *D* shows +++ healing with 4 cc.

+ healing, 3 cc. a complete thin line rated as ++ healing and 4 cc. a thicker complete line rated as +++ healing. In this case one could say that 3 cc. contained 1 Steenbock unit. The level of vitamin D in this serum could be estimated as 33.3 Steenbock, or 110 U. S. P., units per hundred cubic centimeters. Such a test can be considered "complete." Although not too much confidence should be placed in a single estimation, a large number of such complete tests permits the establishment of a reliable average figure.

Results similar to those illustrated in figure 1 could not always be expected, since in the course of some assays difficulties arose which prevented their completion. Some of these difficulties may be cited:

1. Establishment of a complete assay series was impossible because of lack of serum.

2. Sometimes 1 or more rats of a series lost more than 2 Gm. of weight during the test period. Line tests from such animals were discarded, and the valid tests of the series were not sufficient for a complete assay.

3. Sometimes all the rats of a series showed ++ healing (or more), indicating a high level of vitamin D in the serum. If a reserve of serum was not at hand, it could not be ascertained whether the smallest amount of serum fed was actually the smallest dose capable of producing ++ healing.

4. Conversely, none of the rats of some series manifested ++ healing. In this case also the minimum curative dose could not be established unless a reserve of serum was at hand.

5. Occasionally, it happened that in a series a smaller amount of serum produced a higher degree of healing than a larger one, thus disrupting the continuity of the assay.

Under such conditions the assays could not be considered complete, and it was not possible to express the vitamin D content of the assayed serum in units per hundred cubic centimeters. Yet it was felt that the valid tests of these "incomplete" assays should be taken into consideration for the final calculation of the average content of vitamin D of human blood serum. Otherwise, there is the possibility that an exclusion of incomplete tests might lead to a false interpretation of the results.

One example may illustrate this point. If, for instance, a sample was not completed because doses of 1.5 to 4 cc. of serum did not result in ++ healing (and tests with 5 and 6 cc. could not be made because of lack of additional serum), one was probably dealing with a serum low in vitamin D content. If a large number of such serums were among the "incomplete" assays, a large number of serums low in vitamin D would be excluded from the calculation of the average value.

In order to avoid such a possibility, all of the valid line tests obtained from children and adults were considered as derived from one "pooled" sample of blood serum, and the average dose required to produce at least ++ healing in two thirds of the test animals was ascertained. It will be shown later that a fair agreement exists between the results obtained from the complete assays and those derived from all valid line tests.

## RESULTS

From a total of 155 blood samples, 89 "complete" assays were obtained. The values found in these assays are presented in table 1.

The values ascertained in the complete tests ranged between 66 and 165 U. S. P. units per hundred cubic centimeters of serum. The majority of samples contained 110 or 132 U. S. P. units per hundred cubic centimeters. The average level of vitamin D in the serum of all the persons tested was 116.4 U. S. P. units per hundred cubic centimeters.

No striking differences were noted when the results obtained in different subgroups were separated. The only noticeable difference was that between the values for white and those for Negro children. The average value of 122.6 units found for white children was about 15 per

TABLE 1.—*Frequency Distribution of Persons According to Levels of Vitamin D in Blood Serum*

| U. S. P. Units per 100 Cc. of Blood Serum | Total No. Tested | White Adults | White Children | Negro Children |
|---|---|---|---|---|
| 165 | 9 | 2 | 6 | 1 |
| 132 | 27 | 10 | 11 | 6 |
| 110 | 31 | 14 | 10 | 7 |
| 94 | 8 | 2 | 4 | 2 |
| 83 | 13 | 1 | 3 | 9 |
| 66 | 1 | 1 | 0 | 0 |
| Total | 89 | 30 | 34 | 25 |
| Average vitamin D level, units per 100 cc. | 116.4 | 117.6 | 122.6 | 106.5 |

cent higher than the average value of 106.5 units calculated for Negro children. This difference is of interest and is in accord with the familiar assertion that in dark-skinned races rickets develops more easily than in those with lighter skins. Since, however, the average for Negro persons was based on a rather small number of tests, a generalization based on the foregoing results does not yet seem justified.

There was no seasonal variation found by separating the assays of serums taken from May to October, the months in which the effect of sunshine should become manifest, and those taken from November to April.

As previously pointed out, it was considered advisable to check the average value calculated from the complete assays by another method which takes into consideration all the valid line tests obtained by complete and incomplete assays.

Six hundred and eight valid line tests were available for this purpose. Forty-four of these were obtained from rats fed 1.5 cc. of serum; 134 were procured with 2 cc., 149 with 2.5 cc., 160 with 3 cc., 62 with 3.5

cc. and 59 with 4 cc. of serum. In each group a certain percentage of line tests showed ++ healing or more. This percentage increased with the amount of serum administered, as is shown by table 2.

TABLE 2.—*Results of Line Tests Obtained After Feeding Varying Amounts of Normal Human Serums*

| Cc. of Serum Fed | Total Number of Line Tests | Line Tests Resulting in ++ Healing (Or More) | |
|---|---|---|---|
| | | Number | Per Cent |
| 1.5 | 44 | 6 | 13.6 |
| 2.0 | 134 | 36 | 26.9 |
| 2.5 | 149 | 64 | 43.0 |
| 3.0 | 160 | 107 | 66.9 |
| 3.5 | 62 | 50 | 80.6 |
| 4.0 | 59 | 49 | 83.1 |

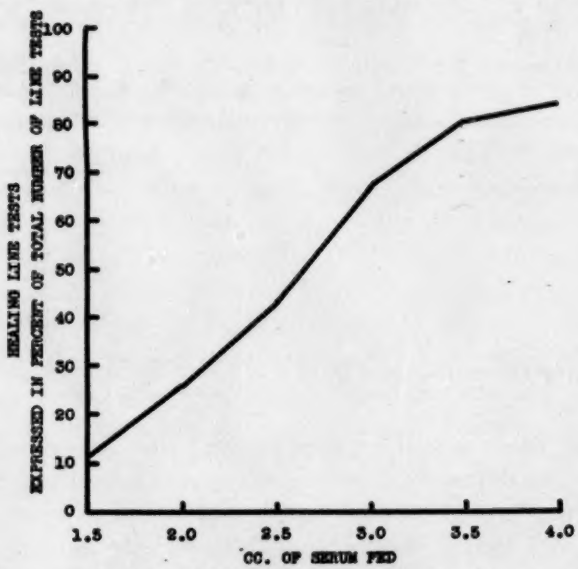


Fig. 2.—Curve showing the relation between the amount of serum administered and the percentage of healing line tests found in all valid line tests.

The curve in figure 2 shows graphically how increasing amounts of serum cause an increasing percentage of healing line tests.

If the curative dose of serum is considered to be that amount which is capable of producing ++ healing in two thirds of the line tests,[9] this amount can be found on the abscissa of the graph in figure 2, at the

9. The curve resembles that obtained with increasing amounts of reference oil described previously. Since 35.1 mg. of the reference oil as well as 3 cc. of serum caused ++ healing in two thirds of the experimental animals as shown by the line test, it can be assumed that these two amounts contain the same quantity of vitamin D. Since 35.1 mg. of the reference oil contains 3.33 U. S. P. units of vitamin D, 3 cc. of serum likewise contains 3.33 U. S. P. units and 100 cc. of serum contains 110 U. S. P. units.

point where the curve reaches the ordinate of 66.6. This value is almost exactly 3 cc. and corresponds to a vitamin D level of 33.3 Steenbock units or 110 U. S. P. units per hundred cubic centimeters of serum. This result agrees satisfactorily with the average obtained from the complete line tests.

## COMMENT

From 89 "complete" bioassays of human blood serum an average vitamin D content of 116 U. S. P. units per hundred cubic centimeters was calculated. When the results of all the valid line tests obtained in this study were taken into consideration, an average vitamin D level of 110 U. S. P. units per hundred cubic centimeters was calculated. It is of interest to compare this value, which is based on 608 line tests, with the vitamin D content of other physiologic materials or foodstuffs.

The substance most frequently tested for its vitamin D content is cod liver oil. Although the oil from livers of individual cod fish may show enormous variations,[10] the average vitamin D content of medicinal cod liver oil can be rated as 10,000 or 15,000 U. S. P. units per 100 Gm.[11] It can be stated, therefore, that human blood serum has approximately one one hundredth the potency of medicinal cod liver oil.

The yolk of hen's eggs has been reported to contain in February and June, respectively, 140 U. S. P. units and 390 U. S. P. units per 100 Gm.[12] Thus the average vitamin D content of egg yolk would be twice that of human blood serum. Butter, which has a vitamin D content of 120 U. S. P. units per 100 Gm.,[11b] has an antirachitic potency equal to that of human blood serum.

Mammalian liver is reported to contain from 10 to 50 U. S. P. units of vitamin D per 100 Gm.,[13] a rather small amount compared to that of blood serum. (The vitamin D content of the serums of a number of mammals tested did not differ greatly from that of man).[14]

The level of vitamin D in cow's milk varies from 0.5 to 4 U. S. P. units per hundred cubic centimeters according to the season.[15] Human

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10. Hess, A. F.; Bills, C. E., and Honeywell, E. M.: Antirachitic Potency in Relation to Volume of Oil in Liver of Cod, J. A. M. A. **92**:226 (Jan. 19) 1929.

11. (*a*) Bills, C. E.: Physiology of Sterols, Including Vitamin D, Physiol. Rev. **15**:1 (Jan.) 1935. (*b*) Coward, K. H., and Morgan, B. G. C.: Quantitative Estimation of Vitamins A and D in Various Food Substances Cooked and Fresh, Brit. M. J. **2**:1041 (Nov. 30) 1935.

12. DeVaney, G. M.; Munsell, H. E., and Titus, H. W.: Effect of Sources of Vitamin D on Storage of the Antirachitic Factor in the Egg, Poultry Sc. **12**: 215, 1933.

13. DeVaney, G. M., and Munsell, H. E.: Vitamin D Content of Calf, Beef, Lamb, and Hog Liver, J. Home Econ. **27**:240, 1935.

14. Warkany, J.: Uber die Bestimmung des Vitamin-D-Gehaltes des Blutserums, Biochem. Ztschr. **293**:415, 1937.

15. Becktel, H. E., and Hoppert, C. A.: Study of Seasonal Variation of Vitamin D in Normal Cow's Milk, J. Nutrition **11**:537 (June) 1936.

milk apparently contains no appreciable amount of vitamin D.[16] Muscle, kidneys and other glandular organs, with the exception of the liver, likewise contain no vitamin D.[17]

It seems, therefore, that blood serum has the highest vitamin D content of all the mammalian materials so far tested.

SUMMARY

An average vitamin D content of 110 U. S. P. units per hundred cubic centimeters of human blood serum was calculated from the results of 608 line tests. In assays of individual blood samples based on a small number of line tests, values between 66 and 165 U. S. P. units should be considered normal. No considerable difference was found in the vitamin D content of serums of adults and children. Marked seasonal variations could not be demonstrated. The values found for white children were about 15 per cent above those obtained for Negro children.

16. Outhouse, J.; Macy, I. G., and Brekke, V.: Human Milk Studies: Quantitative Comparison of Antiricketic Factor in Human Milk and Cow's Milk, J. Biol. Chem. **78**:129 (June) 1928.

17. Eliot, M. M., and Park, E. A.: Rickets, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1937, vol. 1, chap. 36.

# EXPERIMENTAL STUDIES ON IMMUNITY IN DIPHTHERIA

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It is now generally believed that the Schick test is a satisfactory method of determining susceptibility to diphtheria, although a negative reaction is no absolute guarantee against contraction of the disease. Top,[1] in a recent survey of the literature, came to the conclusion that there is no reasonable doubt that a person who reacts negatively to the Schick test will resist ordinary risks of infection. Divergencies between the Schick reaction and the content of serum antitoxin have been reported repeatedly.[2]

Reports on the occurrence of clinical diphtheria in patients with negative reactions to Schick tests are scarce. A review may be found in an article by Underwood.[3] Recently, Morison and Roberts [4] reported on 146 cases of clinical diphtheria among 18,800 prophylactically treated children. Forty of the children affected had negative Schick reactions after the treatment, while 106 had received three injections of immunizing substance but their Schick reaction after treatment was either positive or not ascertained. In 11 of the 40 cases the disease was mild, and in 22 it was of moderate severity.

In former animal experiments [5] I compared the results of the determination of serum antitoxin and of the Schick test with those of a clinical method of detecting susceptibility to diphtheria. This method of testing the resistance of guinea pigs to diphtheria consisted of inoculating the eye with virulent organisms after cauterization of the conjunctiva. There always resulted in control animals a diphtheritic infection, usually followed by the loss of the eye. With this technic, both in actively and in passively immunized animals a serum titer of from 0.03 to 0.05 units of antitoxin per cubic centimeter of blood was shown to protect the eye. A titer of from 0.01 to 0.02 units per cubic centimeter, however, did not prevent infection. In all animals intra-

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The experimental part of this work was performed in the Children's Hospital of the University of Leipzig.

1. Top, F. H.: Arch. Pediat. **54**:480, 1937.
2. Thiele, H.: Arch. f. Kinderh. **94**:175, 1931. Faragó, F.: Am. J. Hyg. **24**: 447, 1936. Jensen, C.: Compt. rend. Soc. de biol. **108**:539, 543, 552, 577 and 579, 1931. Parish, H. J., and Wright, H.: Lancet **1**:600, 1935; **1**:882, 1938.
3. Underwood, E. A.: Lancet **1**:137 and 364, 1935.
4. Morison, A. G., and Roberts, L.: J. Hyg. **37**:388, 1937.
5. Weichsel, M.: Zentralbl. f. Bakt. (Abt. 1) **126**:187, 1932; **129**:177, 1933.

minimum lethal dose. In many instances negative reactions to skin tests with the ordinary strength of toxin—$\frac{1}{50}$ of the minimum lethal dose—were obtained in spite of the fact that the inoculation of the eye produced a diphtheritic infection. A negative reaction obtained with $\frac{1}{10}$ of the minimum lethal dose—five times the ordinary strength of toxin—was indicative of considerable, if not absolute, tissue immunity.

These results might possibly throw some light on the occurrence of diphtheria in persons with negative Schick reactions. It may well be that the test performed in the usual way by injecting $\frac{1}{50}$ of the minimum lethal dose fails in instances of infection with large doses of virulent organisms and thus indicates only relative tissue immunity.

In the animal experiments referred to, 50 to 60 units of diphtheria antitoxin per kilogram of body weight injected subcutaneously was found to protect the guinea pig. In some instances even 5 to 10 units per kilogram of body weight was sufficient to prevent destruction of the cornea. It was further shown that the rate of resorption of diphtheria antitoxin after subcutaneous injection into guinea pigs closely resembled that found after intramuscular injection into human beings. Since the experimental conditions to which the animals were subjected were more unfavorable than those ordinarily encountered in clinical diphtheria, it is possible that a small amount of antitoxin could be sufficient in the treatment of the disease. All that can be done by treatment is to neutralize completely the toxin which is being resorbed. Diphtheria toxin fixed by the tissues before the onset of treatment cannot be neutralized.

From the studies of Schick, Kassowitz and Busacchi [6] it appeared that the intramuscular injection of 100 units of diphtheria antitoxin per kilogram of body weight in about 50 per cent of the patients examined was sufficient to neutralize the effect of the intracutaneous toxin test simultaneously performed. They recommended the intramuscular injection of 500 units of antitoxin per kilogram of body weight in the treatment of diphtheria. Since much smaller amounts of diphtheria antitoxin were shown to neutralize the toxin completely in my animal experiments, the question of how small an amount of antitoxin would neutralize the toxin used in intradermal tests of human beings was investigated.

Children with positive Schick reactions admitted to the ward with tonsillitis were tested in these experiments. They received diphtheria antitoxin because of the diphtheritic appearance of their membranes or in order to test the nonspecific therapeutic effect of horse serum. The serum was given by intramuscular or hypodermic injection. At the time cutaneous toxin tests were performed with $\frac{1}{50}$, $\frac{1}{25}$ and $\frac{1}{10}$ of the

6. Schick, B.; Kassowitz, K., and Busacchi, P.: Ztschr. f. d. ges. exper. Med. **4**:83, 1914.

TABLE 1.—*Influence of Single Subcutaneous or Intramuscular Injections of Diphtheria Antitoxin on the Results of Schick Tests Simultaneously and Subsequently Performed in Children*

| Subject | Age in Years | Units of Diphtheria Antitoxin per Kg. | Method of Injection | Time of Schick Test in Relation to Injection of Antitoxin | Result of Schick Test * |
|---|---|---|---|---|---|
| W. | 5 | 5 | Subcutaneous | 1. Before | + |
| | | | | 2. Simultaneous | — |
| | | | | 3. 24 hr. after | — |
| R. | 4½ | 5 | Intramuscular | 1. Before | + |
| | | | | 2. Simultaneous | Slightly + |
| | | | | 3. 24 hr. after | — |
| J. | 7½ | 5 | Subcutaneous | 1. Before | + |
| | | | | 2. Simultaneous | — |
| | | | | 3. 24 hr. after | — |
| S. | 7 | 10 | Subcutaneous | 1. Before | + |
| | | | | 2. Simultaneous | — |
| | | | | 3. 24 hr. after | — |
| F. | 6 | 10 | Subcutaneous | 1. Before | + |
| | | | | 2. Simultaneous | Slightly + |
| | | | | 3. 24 hr. after | — |
| H. | 5½ | 5 | Intramuscular | 1. Before | + |
| | | | | 2. Simultaneous | — |
| | | | | 3. 24 hr. after | — |
| S. | 7½ | 10 | Intramuscular | 1. Before | + |
| | | | | 2. Simultaneous | — |
| | | | | 3. 24 hr. after | — |
| N. | 3½ | 10 | Intramuscular | 1. Before | + |
| | | | | 2. Simultaneous | — |
| | | | | 3. 24 hr. after | — |
| B. | 5 | 10 | Subcutaneous | 1. Before | + |
| | | | | 2. Simultaneous | — |
| | | | | 3. 24 hr. after | — |
| C. | 6½ | 10 | Intramuscular | 1. Before | + |
| | | | | 2. Simultaneous | — |
| | | | | 3. 24 hr. after | — |
| W. | 4 | 10 | Subcutaneous | 1. Before | + |
| | | | | 2. Simultaneous | — |
| | | | | 3. 24 hr. after | — |
| D. | 5 | 10 | Intramuscular | 1. Before | Strongly + |
| | | | | 2. Simultaneous | — |
| | | | | 3. 24 hr. after | — |
| H. | 3½ | 20 | Subcutaneous | 1. Before | + |
| | | | | 2. Simultaneous | — |
| | | | | 3. 24 hr. after | — |
| L. | 4½ | 10 | Intramuscular | 1. Before | Strongly + |
| | | | | 2. Simultaneous | + |
| | | | | 3. 24 hr. after | Slightly + |
| S. | 6 | 20 | Intramuscular | 1. Before | Strongly + |
| | | | | 2. Simultaneous | + |
| | | | | 3. 24 hr. after | + |
| S. | 7½ | 20 | Intramuscular | 1. Before | + |
| | | | | 2. Simultaneous | — |
| | | | | 3. 24 hr. after | — |
| N. | 7½ | 20 | Intramuscular | 1. Before | + |
| | | | | 2. Simultaneous | — |
| | | | | 3. 24 hr. after | — |
| E. | 3 | 25 | Intramuscular | 1. Before | Strongly + |
| | | | | 2. Simultaneous | — |
| | | | | 3. 24 hr. after | — |
| G. | 3 | 30 | Intramuscular | 1. Before | Strongly + |
| | | | | 2. Simultaneous | — |
| | | | | 3. 24 hr. after | — |
| B. | 5 | 30 | Intramuscular | 1. Before | Strongly + |
| | | | | 2. Simultaneous | — |
| | | | | 3. 24 hr. after | — |
| W. | 4½ | 30 | Intramuscular | 1. Before | Strongly + |
| | | | | 2. Simultaneous | — |
| | | | | 3. 24 hr. after | — |

* Slightly + means erythematous area measuring up to 10 mm. in diameter, with little or no induration; +, erythematous area from 10 to 20 mm. in diameter, with marked induration; strongly +, extensive induration, dusky erythema, occasionally formation of vesicles.

TABLE 1.—*Influence of Single Subcutaneous or Intramuscular Injections of Diphtheria Antitoxin on the Results of Schick Tests Simultaneously and Subsequently Performed in Children—Continued*

| Subject | Age in Years | Units of Diphtheria Antitoxin per Kg. | Method of Injection | Time of Schick Test in Relation to Injection of Antitoxin | Result of Schick Test* |
|---|---|---|---|---|---|
| M. | 8 | 30 | Intramuscular | 1. Before | + |
| | | | | 2. Simultaneous | — |
| | | | | 3. 24 hr. after | — |
| G. | 3½ | 30 | Intramuscular | 1. Before | + |
| | | | | 2. Simultaneous | — |
| | | | | 3. 24 hr. after | — |
| S. | 8 | 30 | Subcutaneous | 1. Before | + |
| | | | | 2. Simultaneous | — |
| | | | | 3. 24 hr. after | — |
| F. | 3½ | 30 | Intramuscular | 7. Before | + |
| | | | | 2. Simultaneous | — |
| | | | | 3. 24 hr. after | — |
| M. | 5 | 30 | Intramuscular | 1. Before | + |
| | | | | 2. Simultaneous | — |
| | | | | 3. 24 hr. after | — |
| D. | 8½ | 30 | Intramuscular | 1. Before | + |
| | | | | 2. Simultaneous | — |
| | | | | 3. 24 hr. after | — |
| T. | 6 | 30 | Intramuscular | 1. Before | + |
| | | | | 2. Simultaneous | — |
| | | | | 3. 24 hr. after | — |
| D. | 4½ | 30 | Intramuscular | 1. Before | Strongly + |
| | | | | 2. Simultaneous | — |
| | | | | 3. 24 hr. after | — |

of the injection a Schick test was done, and for control purposes a second test was performed twenty-four hours later. In all instances concentrated diphtheria antitoxin containing 500 units per cubic centimeter was used in these experiments.

As may be seen, in some children the intramuscular or subcutaneous injection of 5 units per kilogram of body weight was sufficient to neutralize the action of the diphtheria toxin injected intradermally at the same time. An increase in the amount of antitoxin up to 30 units per kilogram produced in all children a negative Schick reaction, even in those patients who had shown a strong reaction prior to the treatment with serum. The Schick test performed twenty-four hours later was constantly negative.

The question of whether larger amounts of intradermally injected diphtheria toxin would be neutralized by the intramuscular injection of correspondingly increased amounts of diphtheria antitoxin was then considered. In former experiments [5] I showed that the law of the multiples of toxin and antitoxin can be proved not only in test tube experiments but also to a certain extent in vivo. Increased amounts of toxin injected intradermally into guinea pigs were neutralized to some extent by proportionally increased amounts of antitoxin. For instance:

| | |
|---|---|
| 50 units per kilogram neutralized | 5 Schick test doses |
| 500 units per kilogram neutralized | 15 Schick test doses |
| 5,000 units per kilogram neutralized | 150 Schick test doses |
| 50,000 units per kilogram neutralized | 1,500 Schick test doses |

As may be seen from these figures, the amount of toxin neutralized increased proportionately to the amount of antitoxin given only with the use of large doses.

The same technic employed in these animal experiments was used with patients with infections of the throat. All of the children were given 500 units of antitoxin per kilogram of body weight by intramuscular injection. At the same time various amounts of toxin were injected intracutaneously. The dose of toxin was gradually increased, since there was uncertainty as to the amount of toxin which would be tolerated. The solutions for the control test had to be increased correspondingly, since the injection of such concentrated solutions of diphtheria toxin tended to produce nonspecific reactions.

TABLE 2.—*Effect of Diphtheria Antitoxin in Doses of Five Hundred Units per Kilogram on Simultaneously Performed Schick Test, Using Multiples of Ordinary Schick Test Dose*

| Subject | Age in Years | Number of Schick Doses | Result of Intradermal Reaction (Modified Schick Test) |
|---|---|---|---|
| S. | 4 | 5 | — |
| W. | 7½ | 7½ | — |
| H. | 8 | 10 | Slightly + |
| W. | 9½ | 10 | Slightly + |
| W. | 6½ | 10 | — |
| H. | 7½ | 13 | Slightly + |
| K. | 10 | 16 | Slightly + |
| S. | 9 | 20 | — |
| H. | 5½ | 33 | — |
| S. | 8½ | 25 | Slightly + |
| H. | 6 | 25 | Slightly + |
| L. | 10 | 50 | — |

It may be seen that on the average at least thirty times the usual Schick dose was neutralized. In one patient even fifty times this dose was tolerated without any local reaction. This suggests that the law of the multiples of toxin and antitoxin may be demonstrated within certain limits in human beings.

## COMMENT

The results seem to confirm the observations made in the animal experiments previously mentioned. The amount of diphtheria antitoxin necessary to neutralize one Schick dose was not higher than 30 units per kilogram of body weight. In many instances much smaller amounts were sufficient. The conclusion may be drawn from animal experiments, as has been demonstrated, that complete neutralization of one Schick dose does not indicate absolute tissue immunity, which is demonstrated only by the neutralization of five times the ordinary Schick dose. It may therefore be that likewise in human beings only the negative reaction to five times the ordinary Schick dose shows immunity against even

severe infection with virulent Bacillus diphtheriae and that the occasional occurrence of diphtheria in persons with negative Schick reactions may thus be explained. As has been shown in table 2, increased amounts of toxin are tolerated when accompanied by the injection of proportionally increased amounts of diphtheria antitoxin. Since in all instances one Schick dose was completely neutralized by the subcutaneous or intramuscular injection of from 30 to 50 units of antitoxin per kilogram of body weight, one may assume that for the neutralization of five Schick doses an amount of from 150 to 250 units per kilogram of body weight is sufficient. This is to be considered an optimal dose. It is similar to that originally suggested by Schick and his co-workers.

## SUMMARY

The intramuscular injection of from 30 to 50 units of diphtheria antitoxin per kilogram of body weight is sufficient to neutralize the effect of the intradermal test simultaneously performed with $\frac{1}{50}$ of the minimum lethal dose of toxin.

An increase in the amount of diphtheria antitoxin injected intramuscularly leads to a proportionally increased neutralization of diphtheria toxin injected intradermally when large doses are used.

There is no experimental evidence for increasing the amount of antitoxin injected for therapeutic purposes beyond the optimum of from 150 to 250 units per kilogram of body weight.

Dr. Philip Cohen gave aid and advice in the preparation of this report.

# EFFECT OF FETAL ACTIVITY ON THE NUTRITIONAL STATE OF THE INFANT AT BIRTH

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During the past ten years the work of the Samuel S. Fels Research Institute has included a study of the growth, physiology and nutrition of the human fetus in utero. During this period my associates and I, in addition to collecting and publishing a considerable amount of research data, have made certain observations on fetal nutrition which I believe to be both interesting and significant. These observations have led to the formulation of the following hypothesis: The degree of intrauterine fetal activity or movement may be an important factor in the storage of fat by the fetus and therefore in the weight and state of nutrition of the newborn infant, and there are extrauterine factors, that might be called factors of prenatal environment, which are extremely important in stimulating the fetus to muscular movement and in consequently influencing the state of fetal metabolism and nutrition. Although the process of accumulating conclusive evidence to prove or disprove the hypothesis is long and not complete, I believe that it is desirable to present the hypothesis, together with such evidence for it as is now available.

It is customary to look on the human fetus as a parasite—a creature which during almost all of its nine months of intrauterine life takes what it needs for growth and maintenance from the body of its host, the expectant mother. This relation is such that little concern that the fetal needs will not be cared for is felt. Fetal rickets probably does occur but only when the mother is suffering from a severe degree of starvation. Maxwell and Miles [1] and others have reported the occurrence of fetal rickets in children of starving Chinese women. In mothers with a diet which is curtailed, but not so severely as to produce fetal rickets, there may, of course, be inadequate storage of vitamins. However, these difficulties probably occur only when the maternal diet is rather drastically limited, usually either by extremely low economic status or by prolonged illness. Specifications of diet as a part of prenatal care are ordinarily concerned much more with the protection of

From the Samuel S. Fels Research Institute, Antioch College.

1. Maxwell, J. P., and Miles, L. M.: Osteomalacia in China, J. Obst. & Gynaec. Brit. Emp. **32**:433, 1925. Maxwell, J. P.: Vitamin Deficiency in the Antenatal Period: Its Effects on the Mother and Infant, ibid. **39**:764, 1932.

the maternal system against depletion than against possible fetal deficiency. Such relative independence of fetal demands of maternal food intake (except, as has been indicated, in extreme cases) is based on the fact that the mother tends to keep minerals, carbohydrates and amino acids at more or less constant levels in the blood through the utilization of stores of these materials which may be depleted or replenished according to the dietary intake and nutritional demand. So long as these stores are sufficient to maintain usual levels in the maternal blood, the source of fetal nutritive elements should be safe.

The next problem to be considered in fetal nutrition is that of transportation or transmission of nutritive elements from the maternal circulation into the fetal circulation. The entry of nutrient elements and the elimination of waste products is, of course, accomplished through the medium of the placenta. Because of the maternal stores, the source of food available for fetal needs is great, with a vast margin of safety over usual fetal requirements. "Importation facilities"—the means by which the placenta transmits supplies of food from the maternal to the fetal circulation—do not, however, afford such a broad margin of safety. All, or nearly all, of the capillary area of the placenta is used for the normal nutrition of the growing fetus. There is much evidence for this conclusion. Adair and Schumann [2] stated:

> The nutrition of the fetus is very important in determining its size. It is not known just how much the development of a fetus can be influenced by maternal diet but probably not to any great extent unless the mother is placed upon an actual deficiency regimen. There are other factors of definite importance, such as the implantation process. It has been shown by Adair and Thelander [3] that there is a definite relationship between the size of the placenta and the size of the fetus. Another factor is the condition of the placenta, which frequently is the site of retrogressive changes. One cannot tell just what the margin of safety in the placenta is, but one author has seen a few cases in which a small fetus was born, apparently at term, in which half of the substance of the placenta appeared degenerated. It seems probable that a decrease in the size of the functioning placenta would curtail the food supply of the fetus and result in the birth of a smaller infant. . . . The condition which stunts . . . the fetus is probably a placental deficiency or insufficiency. This is well illustrated in twin pregnancies in which one fetus receives the larger blood supply from the major portion of the placenta. The one whose vascular system is connected with the smaller portion of the placenta may be smaller than its mate and may even succumb.

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2. Adair, F. L., and Schumann, E. A.: Anatomy, Physiology and Pathology of the Fetus, in Curtis, A. H.: Obstetrics and Gynecology, Philadelphia, W. B. Saunders Company, 1933, vol. 1, pp. 513-556.

3. Adair, F. L., and Thelander, H.: Weight and Dimensions of Human Placenta in Its Relation to Weight of Newborn Infant, Am. J. Obst. & Gynec. **10**:172, 1925.

The inequality in the size of monozygotic twins and the relation of this inequality to unequal blood supplies are well known. The fibrotic placenta, with its infarcts and the resulting small infant, which is often seen in severe preeclampsia and nephritic toxemia, is also familiar phenomenon.

This discussion of placental capacity is, of course, based on the assumption of a maintenance of nutrient substances in the fetal blood at or near a constant level. The situation might be summarized as follows: Approximately the full capacity of the placenta is required to meet the normal requirements of the fetus. The flow of food elements across the placenta will not be appreciably increased unless there is either an increase in the level of these substances in the maternal blood or a decrease of them in the fetal blood. The level of dextrose maintained in the fetal blood is independent of requirements for storage. It must be emphasized that there is no active mechanism for the deposition of stores of subcutaneous fat. Such fat is probably a storage of converted glycogen or possibly of fatty acids not required for immediate burning (Wesson[4]). It is a storage of energy-producing foods not needed for immediate consumption and is accomplished without the reduction of blood sugar below its normal physiologic level. The mechanism maintaining the blood sugar level should not be affected appreciably by a shift toward greater fetal consumption of glycogen and lessened synthesis of fat, and there should be, therefore, no major changes in osmotic pressure on the fetal side which could lead to an increased passage of dextrose. Maternal diabetes provides an excellent example of the fact that fetal blood sugar levels are usually independent of the fetal requirement for sugar. In this condition, because of constantly high maternal blood sugar levels, more sugar passes over into the fetal blood. Since it is not needed, it is stored as fat. It is for this reason that children of diabetic mothers are usually heavy.

The source of fetal food, then, is ordinarily almost unlimited, but the transmitting system has little reserve—it is utilized at or near its full capacity as long as blood sugar levels are not changed sufficiently to affect the rate of diffusion. This brings up the third point in this critical subject of fetal nutrition, namely, the matter of fetal requirements. The food requirements of the fetus are threefold: (1) for growth, (2) for maintenance and (3) for energy. The requirements for growth are, of course, principally a matter of storage. Maintenance of the fetus is probably not vastly different from maintenance of the bodily structure of the young infant, and it may be assumed that there is no great individual variability in requirements except in relation to fetal age and to weight. The requirement for maintenance has been calculated. The requirement for energy, however, is one to which

4. Wesson, L. G.: Fetal Synthesis of Fats, Bull. Johns Hopkins Hosp. **38**: 237, 1926.

entirely inadequate consideration has been given. This lack of appreciation of the differences in the energy requirements of fetuses and the part they may play in the entire economy of fetal nutrition arises from a lack of knowledge of the great differences there may be in the physical activity of fetuses and of the factors which influence or control that activity.

It is easy enough to approximate the amount of calcium and phosphorus necessary for the production of an 8 pound (3.6 Kg.) fetus by the simple chemical analysis of a few stillborn children. It is easy, of course, to make a quantitative determination of the storage of fat or glycogen. Such figures for fat and glycogen, unlike those for minerals, tell only the quantity of these substances actually on hand at birth. The quantity of food needed for fuel is, however, dependent on the amount of energy expended. Maintenance of heart beat is a need of more or less constant proportions and has been estimated by physiologists at about 1.8 calories per kilogram per twenty-four hours. Carpenter and Murlin,[5] by a calorimetric technic, have calculated the average total production of heat by 3 fetuses. No figures are available, however, which show the degree of variability of fetal heat production.

The question of the significance of this variable requirement for energy in fetuses and the part that it will play in determining physical state at birth may now be considered. With a given food supply, determined by placental size and location and by the levels of nutrient elements in the maternal and fetal blood, an inactive fetus—one whose metabolic processes are slow and whose food requirements are consequently low—will store a major portion of the materials. A fetus which is active, however, will require a much larger quantity of food for energy and will, in consequence, be able to store much less. Such a situation will result in a newborn child of normal length but with an abnormally low supply of body fat.

While normally the human fetus probably derives its energy from dextrose, and fetal fat is largely synthesized from the same substance, when the requirement for energy is such that all the available glycogen is still not adequate it is probable that the fetus then uses available fats or fatty acids. It is even conceivable that in extreme circumstances amino acids may be burned to produce the necessary calories and thus decrease the amount of these "building stores" available for the construction of muscle and other structures in which nitrogen is an essential part. The most rapid increase in weight and most of the deposit of fat occur during the last eight weeks of intrauterine growth. Therefore, fetal activity before the last eight weeks would not cause a child to be deficient in fat. It is possible, however, that a fetus might, in response

5. Carpenter, T. M., and Murlin, J. R.: Energy Metabolism of Mother and Child Just Before and Just After Birth, Arch. Int. Med. 7:184 (Feb.) 1911.

to certain stimuli, develop a pattern of activity which would remain for some time after the stimulation had ceased. If this is true, then environment which stimulated activity at the seventh month might influence the state of the infant at birth.

The question now arises as to how much difference there actually is in the activity and, therefore, the energy requirements of fetuses. At the Samuel S. Fels Research Institute, we have had an excellent opportunity for studying this problem. We have had under observation during the latter half to two thirds of pregnancy approximately 140 women. A part of this group has been used for a study of fetal activity during several hours each week for the third trimester. Actual samplings of fetal activity have ranged from three hours per week to fifteen or more hours per week. Two different methods of recording have been used (Sontag and Wallace [6] and Richards and associates [7]).

These observations, a statistical analysis of which has been published (Richards and associates [7]), show a variation of roughly 1,000 per cent in the group in the mean number of minutes during which the fetus moved one or more times in the samplings over a three month period. For example, the least active fetus was active in 7 per cent of the forty-five hundred minutes it was observed during a three month period, while the most active fetus showed one or more movements in 70 per cent of a similar period. Since one movement during a given minute makes the minute "active" and additional movements during the same minute do not increase the scoring, the actual difference in activity is probably even greater. An analysis of total movements bears out the observation that differences between fetuses are even greater than 1,000 per cent. That the difference in heat production between active and relatively inactive fetuses is considerable is indicated by the work of Richards and associates,[7] who found a relation between the activity of fetuses and the rise in maternal basal metabolic rate, although there was no demonstrable relation between early basal metabolic rates and later fetal activity. The greater rise in heat production of some mothers appeared to be due at least in part, therefore, to the greater heat production of their more active fetuses.

Obviously, degree of activity is not the only factor which affects the weight of the fetus. Heredity is probably an important factor. Maternal endocrine function may be another. Maturity of the fetus, as indicated by total length, of course, and location of the placenta are important. Since there are obviously several factors which influence

6. Sontag, L. W., and Wallace, R. F.: An Apparatus for Recording Fetal Movements, Am. J. Physiol. **45**:517, 1933.

7. Richards, T. W.; Newberry, H., and Fallgatter, R.: Studies in Fetal Behavior: II. Activity of the Human Fetus in Utero and Its Relation to Other Prenatal Conditions, Particularly the Mother's Basal Metabolic Rate, Child Development **9**:69, 1938.

the weight of the fetus and since there is no way of appraising or correcting for most of them, it is impossible to determine in any one newborn child exactly how much or how little its prenatal activity has affected its storage of fat. Although one cannot correct for most of these factors, we have nevertheless determined the correlation between birth weight and fetal activity during the last two lunar months of intrauterine life, correcting only for maturity by taking length into consideration. We have used two different formulas for correcting for length, namely, $\frac{\sqrt[3]{\text{weight}}}{\text{length}}$ and $\frac{\text{weight}}{\text{length}^3}$. The use of one or the other of these formulas is essential, because increase in weight is a cube function

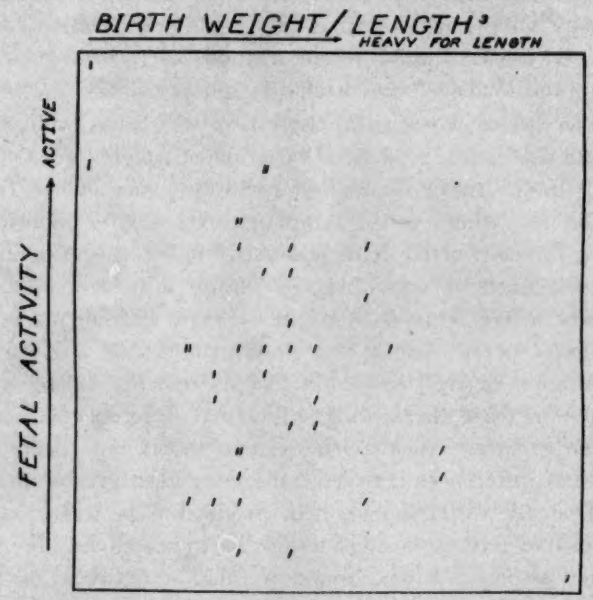


Chart 1.—Scatter plot of 38 cases, with fetal activity plotted against $\frac{\text{weight}}{\text{length}^3}$ of the child, showing that (1) light babies may have been either active or inactive fetuses, (2) inactive fetuses when born may be either light or heavy babies, (3) no heavy babies had been active fetuses and (4) no active fetuses when born were heavy babies.

of increase in length. In other words, an animal which doubles its length will much more than double its weight, for while length is a one-dimensional growth, increase in weight is three-dimensional. Correlating birth weight with fetal activity, using the first formula, yields a Pearson r of $-0.35$; using the second formula does not essentially alter the results and yields $r = -0.37$. Thirty-eight cases constitute the material for this correlation. These figures, while they are derived from a small group of cases, indicate that as fetal activity tends to increase, weight of the newborn child tends to decrease.

Chart 1 is a scatter diagram of the 38 cases, with activity plotted against $\frac{\text{weight}}{\text{length}^3}$. From the diagram the following facts are evident:

1. Light babies may have been either active or inactive fetuses. Inactive fetuses may be either light or heavy babies at birth. These two facts are evidenced by the distribution of cases in the lower left corner of the diagram. This type of distribution would be expected, because, as already pointed out, there are many factors other than fetal activity which affect the weight of the newborn child.

2. However, no heavy babies had been active fetuses and no active fetuses were heavy babies at birth. There is no distribution of cases in the upper right corner of the diagram. Apparently, active fetuses cannot store large quantities of fat. Fetuses may become heavy only if they are relatively inactive.

It now becomes important to consider what prenatal environmental factors are capable of altering the activity of the fetus to the degree of producing a strain on its nutritional supply. In general, environment has been more or less habitually thought of as something which becomes effective only at birth. Such an idea is, however, erroneous. Feldman,[8] citing Féré, stated that all fetal movements are of reflex origin. According to him, numerous stimuli, including loud sounds, fatigue and maternal emotions, cause a uterine contraction, which in turn stimulates the fetus to muscular movement. While we have observed the same phenomenon in many of our patients, we believe that the fetus' response to loud noise is caused directly by its perception of sound.

The fetal reaction to maternal emotion we believe to be in response to an accentuated maternal endocrine secretion (preliminary experiments suggest it may be epinephrine). In the case of maternal fatigue, the response may be to the transmission of accumulated waste products. We have reported certain of our findings in this field (Sontag and Wallace[9]). We are convinced that sound, emotion and fatigue as stimulants to the muscular activity of the fetus are matters of everyday occurrence. While fatigue did increase fetal activity in the group under observation, it did not ordinarily cause an increase of such proportions as to produce a recognizable disturbance of the nutritional state of the fetus. Noisy washing machines, musical concerts and loud radio music have all been known to produce a period of much heightened activity. Such stimuli are usually intermittent, however, and may be effective only for a few hours a week. Under these circumstances, they are unlikely to disturb fetal nutrition enough so that the effect can be recognized at birth. In instances of more or less constant

8. Feldman, W. M.: Antenatal and Postnatal Child Physiology, London, Longmans, Green & Co., 1920, p. 207.

9. Sontag, L. W., and Wallace, R. F.: Preliminary Report of the Fels Fund: Study of Fetal Activity, Am. J. Dis. Child. **48**:1050 (Nov.) 1934.

auditory stimulation, however, there is no reason to believe that an alteration of the fetus' nutritional state could not result. Emotional disturbance of considerable severity, prolonged over a considerable period, is, of course, seen not infrequently. Because many pregnancies are unwanted, because pregnancy is for the primigravida a new and unknown experience and because it imposes additional economic burdens, emotional upsets are probably more common to women during pregnancy than under ordinary circumstances. For these reasons, emotions may be important factors in determining the level of fetal activity and, therefore, the state of fetal nutrition. The following cases illustrate the apparent relation between the maternal emotional state and the state of nutrition of the fetus at birth.

## REPORT OF CASES

CASE 1.—The mother was an unmarried white woman aged 33 who was 5 feet tall (152 cm.) and weighed 102 pounds (46.3 Kg.). Her physical condition was good except for a rather high basal metabolic rate throughout pregnancy. The hemoglobin content did not drop below 74 per cent, and the urine remained free from albumin and sugar throughout. Her gain in weight during pregnancy was 12 pounds (5.4 Kg.).

She was of a rather nervous temperament and was easily disturbed. The father of her child had concealed from her the fact that he already had a wife and family until after she had become pregnant. Her background was strongly religious and moralistic, and she had a highly developed sense of her responsibility to the child. Coupled with this situation was the fact that she was under the care of an elderly woman who constantly made life miserable for her because of the difficulty she had got herself into. The product of this situation was a state of almost continual emotional turbulence.

The fetus was extremely active at almost all times (active during 53 per cent of the minutes observed during the last six weeks of pregnancy). During a period of three weeks when her agitation was even more heightened, 73 per cent of the recorded minutes showed activity. The baby was born at term, after a labor of fourteen hours and by a low forceps delivery. It was 46.8 cm. in length and weighed 5 pounds 12 ounces (2,608 Gm.). It showed no evidence of immaturity. The subcutaneous fat was extremely scarce, and the legs and arms were of small diameter. The skin was more than usually wrinkled. The child was extremely active and irritable.

CASE 2.—The mother, white, aged 25, had been married for four years. Her physical condition was good. Her weight before pregnancy was 125 pounds (56.7 Kg.), and her gain during pregnancy was 16 pounds (7.3 Kg.). The laboratory findings were not remarkable.

She and her husband were both college graduates. Her husband had shown previous indications of a not too stable emotional constitution, and during the fifth month of his wife's pregnancy he displayed definite manic symptoms. He became more or less constantly irritated at his wife and struck her on several occasions. During the balance of the pregnancy his condition became worse. The wife lived in constant apprehension of physical violence and, since they had little financial reserve, was, in addition, faced with the problem of providing for the care of a newcomer in the family, as well as with deciding what course to pursue in regard to her husband's psychosis.

On several occasions when her husband became quarrelsome and threatened her, she left her home for the night and sought refuge with friends. At such times she complained of being unable to sleep because of the violence of the movements of the fetus and of soreness of abdominal muscles from this violent activity. The fetus was extremely active throughout the entire last half of pregnancy. At birth the infant was 52 cm. long and weighed 6 pounds 8 ounces (2,948 Gm.). It was mature but had an inadequate layer of subcutaneous fat. Its legs and arms were like pipestems. It was extremely active and irritable.

Both these infants started life well below the average in weight in relation to both height and age. In case 1 there was a rapid development of subcutaneous fat and a rapid gain in weight, so that by 9 months of age the child had reached the group median and by 12 months it was well above the median in weight for both age and height. The

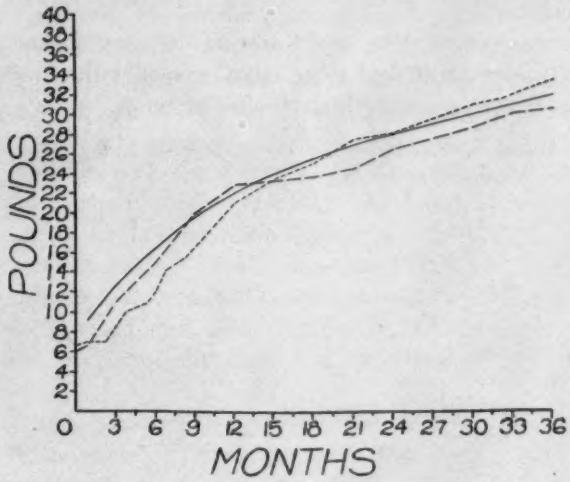


Chart 2.—Weight curves of the infants of 2 mothers undergoing severe emotional strain during pregnancy. The weight norm for the Fels group of boys is indicated by the solid line. The rapidity with which the weight trends change after the first few months is of interest.

child in case 2 did not catch up until it was 12 months of age. It went well beyond the median in weight for age thereafter. The progress in weight of the 2 children in relation to group norms is shown in chart 2. The marked change indicated in these children's weight charts suggests that their low birth weights did not reflect a constitutional tendency and that when their sources of nutrition were changed at birth, their body types underwent marked alteration also.

## SUMMARY

Available evidence indicates that while the initial source of energy-producing foods for the human fetus is normally almost unlimited, the

system of placental transmission may limit the amount of glycogen and fatty acids available for fetal needs.

Active and frequent fetal movements require the consumption of considerable amounts of energy-producing foods which might otherwise be stored as fetal fat. Excessive fetal activity may, therefore, be responsible for infants who are considerably underweight for their body length.

Many factors influence fetal activity, among them sounds, maternal fatigue and maternal emotion. Maternal emotion, possibly through the liberation of epinephrine, seems to exert a strong influence on activity of the fetus over long periods. Two illustrative cases are reported in which severe and prolonged maternal emotional disturbance may have been an active factor in producing the undernourished appearance of 2 newborn infants.

The environment of the infant during its intrauterine life is a subject worthy of a great deal more study, consideration and, perhaps, concern than has customarily been bestowed on it.

Dr. T. W. Richards, Miss Helen Newberry and Miss Ruth Fallgatter collected many of the data presented in this paper.

# EVALUATION OF THE TUBERCULIN PATCH TEST

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AND
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In 1937 Vollmer and Goldberger [1] described a new tuberculin patch test and compared its results with those of the Pirquet test in 209 tuberculous children. Their study showed conformity of results in 187 patients, or 89.5 per cent, and nonconformity in 22, or 10.5 per cent, with 15 of the latter reacting positively to the patch test and negatively to the Pirquet test. From the point of view of reliability, this new test was considered superior and had the added advantage of simplicity.

In the following year these authors [2] published observations on 169 tuberculous children, employing for the patch test tuberculin [3] approximately four times stronger than that originally used, and compared the results with those of the Mantoux intracutaneous test, using purified protein derivative. Only 1 child failed to react to the patch test who at the same time reacted positively to the intracutaneous test. In a subsequent study [4] of 417 unselected children they reported the reliability of the patch test as compared with the Mantoux test, using 0.1 mg. of old tuberculin, to be practically 100 per cent; only 4 results showed lack of conformity, and 3 of these were positive reactions to the patch test.

Hart [5] and Steward [6] published similar results, but Weiner and Neustadt [7] and Court [8] found the patch test slightly less reliable than

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From the Allergy Clinic, Sydenham Hospital.

1. Vollmer, H., and Goldberger, E. W.: A New Tuberculin Patch Test, Am. J. Dis. Child. **54**:1019 (Nov.) 1937.

2. Vollmer, H., and Goldberger, E. W.: Comparative Study of the Tuberculin Patch Test and the Mantoux Intracutaneous Test, Am. J. Dis. Child. **56**: 584 (Sept.) 1938.

3. Tuberculin prepared with the use of a synthetic medium according to the formula of Seibert (The Isolation and Properties of the Purified Protein Derivative of Tuberculin, Am. Rev. Tuberc. **30**:713 [Dec.] 1934).

4. Vollmer, H., and Goldberger, E. W.: Evaluation of the Tuberculin Patch Test (Vollmer-Lederle), Am. J. Dis. Child. **57**:1272 (June) 1939.

5. Hart, F. D.: Tuberculin Patch Test in Children, Lancet **2**:609 (Sept. 10) 1938.

6. Steward, W. D.: The New Tuberculin Patch Test, J. Pediat. **13**:510 (Oct.) 1938.

7. Weiner, S. B., and Neustadt, A.: Tuberculin Patch Test, J. Pediat. **14**: 752 (June) 1939.

8. Court, D.: A Comparative Study of the Tuberculin "Patch Test" and the Intracutaneous Mantoux Test in Childhood, Brit. M. J. **1**:824 (April 22) 1939.

the intracutaneous test (using 0.1 mg. of old tuberculin), although the results of the two tests were at least in agreement in from 95 to 98 per cent of the trials. Peck and Weyman,[9] however, in comparing the Vollmer patch test with that performed with purified protein derivative (purified protein derivatives I and II) injected intracutaneously, obtained only 30 per cent as many positive reactors with the former method and concluded that the patch test was unreliable as a diagnostic procedure for public health work among children of school age.

We became interested in the tuberculin patch test because in our work at the children's allergy clinic of the Sydenham Hospital we routinely perform Pirquet and Mantoux tests, the latter being done, with 0.1 mg. of old tuberculin, when the Pirquet test is negative. In order to determine the reliability of this test, the children studied in this investigation included unselected patients from the wards and outpatient department, as well as those from the allergy clinic.

## MATERIAL AND METHODS

Three hundred and thirty children, ranging in age from 4 months to 14 years, were studied. Eighty-eight attended the allergy clinic and 126 the pediatric clinic, and 116 were inpatients of the hospital. Fifty-four per cent of the entire series were Negro or Puerto Rican, and practically all the children were from indigent or low income families. The condition of 8 was diagnosed as tuberculosis; the others were suffering from a great variety of diseases. Roentgen examination of the chest was performed on nearly all patients who reacted positively to tuberculin.

The Pirquet test with old tuberculin[10] was performed first, on the upper and outer part of the volar aspect of the forearm. Forty-eight hours later the test was read, and, if negative, a tuberculin patch test[11] and Mantoux intracutaneous test (0.1 mg. of old tuberculin) were simultaneously performed. The latter was done on the upper and inner part of the same forearm and the patch applied longitudinally in the lower half of the forearm. In young children the patch was sometimes placed in the interscapular region. Alcohol was used to cleanse the skin before application of the patch. Occasionally, extra strips of adhesive tape were employed to insure adequate contact, and bathing of the part was prohibited until after the test was read. Readings were made in forty-eight hours and as late as from four to seven days. Irritation from adhesive tape occurred in some instances but usually disappeared within twenty-four hours after removal of the patch. In 6 instances dermatitis resulted from the adhesive tape.

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9. Peck, E. C., and Weyman, M. E.: Comparison of the Vollmer Tuberculin Patch Test with Purified Protein Derivative, J. Pediat. **15**:219 (Aug.) 1939.

10. The old tuberculin used for the Pirquet and Mantoux tests in this study was supplied by the Department of Health of the city of New York.

11. The material for the patch test was supplied by the Lederle Laboratories. Approximately two thirds of the patches used were made with old tuberculin, the remainder with the more concentrated tuberculin prepared with a synthetic medium.

*Reading of the Patch Test.*—The test was read as positive or negative. Positive reactions were further classified as follows:

One plus (+)—a faintly erythematous area, sharply defined, slightly elevated and corresponding in size to the tuberculin-treated square, with fine pinpoint elevations or vesicles.

Two plus (++)—a more markedly erythematous area, definitely elevated above the surrounding surface, with several small vesicles in addition to pinpoint elevations in the square and some erythema in the surrounding area.

Three plus (+++)—a marked, irregular elevation extending beyond the size of the original patch, surmounted by numerous vesicles and occasional large blebs, with moderate induration in the periphery.

A negative reaction differed in no way from the result of the control patch test.

In some instances a test resulting in a faint erythema or negative reaction after forty-eight hours became definitely positive when read ninety-six hours or more after the application of the patch. The 1 plus and 2 plus reactions subsided and disappeared, usually, in from two to three weeks; the 3 plus reactions

*Comparative Results of the Pirquet, Patch and Mantoux Tests*

| Number of Patients | Pirquet Test | Patch Test | Mantoux Test* | |
|---|---|---|---|---|
| | | | — | + |
| 273 | — | — | 267 | 6 |
| 14 | — | + | 3 | 11 |
| 40 | + | + | ... | .. |
| 3 | + | — | ... | .. |
| Totals 330 | | | | 287 |

* The Mantoux test (0.1 mg. of old tuberculin) was done only when the result of the Pirquet test was negative.

persisted for from four to six weeks. The reactions to the Mantoux and those to the patch tests disappeared after approximately the same time.

The patch test caused no discomfort except for slight pain and itching at the site in some of the children with 2 and 3 plus reactions.

## RESULTS

The accompanying table shows corresponding reactions obtained with the Pirquet, patch and Mantoux tests. Results of the Pirquet and patch tests agreed in 313 patients, or 95 per cent, and disagreed in 17, or 5 per cent. Of these 17 patients 14 had positive reactions to the patch test and negative to the Pirquet test. Eleven of the 14 also showed a positive reaction to the Mantoux test (0.1 mg. of old tuberculin), and 7 revealed roentgenographic evidence of increased markings in the hilus or changes in the parenchyma of the lungs. On the 3 patients who reacted negatively to the patch test and positively to the Pirquet test no intracutaneous test was done, and roentgen examination of the chest gave negative results. A total of 54 positive reactions was obtained with the patch test, as compared with 43 with the Pirquet test.

Results of the patch and Mantoux tests agreed in 278 patients, or 97 per cent, and disagreed in 9, or 3 per cent. Six of the 9 children

reacted negatively to the patch test and positively to the Mantoux test, a result which was confirmed on retesting. Roentgen examinations of the chest of these 6 patients showed increased pulmonary markings, with calcified deposits in 3, miliary tuberculosis in 1 and no pathologic changes in 2. Three children showed a positive reaction to the patch test and a negative reaction to the Mantoux test. In all, 17 positive reactions to tuberculin were elicited with the intracutaneous test against 14 with the patch test among the 287 children given both tests.

## COMMENT

The type of reaction elicited with the tuberculin patch test is not unlike that obtained with patch tests performed with plant and pollen oils, drugs, chemicals, metals and a great variety of nonprotein substances in the diagnosis of contact dermatitis. The reaction is characterized by erythema and vesiculation and differs from the indurated, inflammatory reaction following a Pirquet or a Mantoux test.

According to Zinsser, tuberculin contains two definite substances, one the carbohydrate "residue" material and the other the nitrogenous, possibly protein, material which is responsible for the effects of tuberculin. In recent years Siebert, using a synthetic culture medium and purifying tuberculin by means of ultrafiltration and precipitation, removed the loosely combined polysaccharide and thus obtained a purified protein derivative which has been shown quantitatively to be much more active than old tuberculin when used in either the Pirquet or the Mantoux test. However, for the patch test the purified protein derivative has been found to be less active than old tuberculin. While this may be due to differences in solubility or absorption through the unabraded skin, as suggested by Vollmer,[12] one must consider the possibility that the process of purification has removed some of the substance responsible for the contact type of reaction. Patch testing with the nonprotein fraction of tuberculin would make an interesting study and might throw some light on this question.

## CONCLUSIONS

From this study of 330 children one may conclude that the tuberculin patch test is a simple, practical and reliable test, somewhat more sensitive than the Pirquet test and slightly less sensitive than the Mantoux test (0.1 mg. of old tuberculin).

For routine work it may be recommended as the initial test in place of the Pirquet, and if the result is negative at the end of one week, a Mantoux intracutaneous test with 0.1 mg. of old tuberculin should be performed.

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12. Vollmer, H., and Goldberger, E. W.: Old Tuberculin and Purified Protein Derivative in the Tuberculin Patch Test, Am. J. Dis. Child. **58**:527 (Sept.) 1939.

# A SIMPLE MECHANICAL AID IN THE TREATMENT OF ACUTE RHINITIS OF INFANCY

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Acute coryza in infancy, with its tendency to complications, demands serious consideration. The lack of effectiveness of the various types of nose drops, especially in the treatment of infants with considerable drainage, led to a search for an effective method which might be used to clear the nasal passages mechanically.

For the past three years I have used a soft rubber ear syringe, inserted into the nostril. The bulb, compressed before introduction, is then allowed to expand, thereby withdrawing the offending material. By allowing the opposite nostril to remain open there is no danger from an excessive negative pressure. The mother or nurse is especially cautioned against exerting positive pressure.

The results from the use of the syringe have been gratifying, especially in those instances in which the infant could not take the breast or bottle because of inability to breathe as a result of the mechanical plugging of the nose with secretion. A treatment immediately before feeding time often results in the child's being able to take nourishment much more readily. Treatments may be given as often as necessary.

After the suction treatment nose drops, such as ephedrine sulfate or neo-synephrin hydrochloride, according to the preference of the physician, may be used, and as they will then be in direct contact with the tissues they will be much more efficacious.

As would be expected, when the reaction is preponderantly edematous, with little or no drainage, this method is not effective.

# RELATIVE EASE OF INTERFERENCE WITH GROWTH AND DEVELOPMENT IN THE GUINEA PIG

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Anthropometric examinations of supposedly healthy children or of those brought to the physician because of illness show wide variations in individual children from the so-called standards of height, weight and maturity which are in common use. Not only may a child be advanced or retarded in growth and development as a whole, but the various components often vary so that the individual child may be, for example, of standard height, markedly deficient in weight and advanced in maturity. Evidently growth in height, increase in weight and advance in maturity, while integrated in the growing organism, require either different types or different degrees of interference to alter their rates of progress.

The standards for comparison as pointed out in the publications of the White House Conference [1] are by no means exact when applied to any child, as they represent a mean for each measurement, determined on children who may be functionally adequate but far below optimal functional potentiality. They represent, in fact, a "mediocre mean," and variations from them must be interpreted in terms of hereditary body build, rate of growth, rate of development and nutritional adequacy.

A single examination of any child determines his status at that time. Subsequent examinations at intervals enable one to compare the actual progress with that expected and to observe variations between increments in the various components of growth and development.

In this manner one is able to evaluate, at least in part, the reasons for the deviations from the standards which were observed at the time of the first examination. Such an evaluation requires first an appreciation of the difference between growth, which is increase in size, and development, which is progress toward maturity, and second some knowledge of the relative ease with which the orderly progress of each of these components can be altered. This knowledge is not easy to obtain in children because of the difficulty in assessing the familial

From the Asthma, Hay Fever and Allergy Foundation.

1. Growth and Development of the Child: IV. Appraisement of the Child, White House Conference on Child Health and Protection, New York, Century Company, 1932.

pattern and controlling the dietary and environmental factors. The diet and the environment can be controlled in experimental animals, however, and in these familial pattern is much less variable than in human beings.

Since disturbances in growth and development must be due to malnutrition in its broadest sense, the following nutritional experiments were undertaken to determine, if possible, the relation of the various components and the ease or difficulty of interference with them.

One male and 39 female guinea pigs were purchased from a reliable source. They weighed about 250 Gm. each and were from 6 to 8 weeks old. They were fed for two weeks on alfalfa hay, sprouted oats, carrots and lettuce. At the end of two weeks they were weighed and roentgenograms were made to determine state of nutrition, length of bone and maturity by comparison with the standards developed by Zuck [2] in his six year study of growth and maturity in the guinea pig using this diet. The animals were then transferred to the scorbutogenic Demole [3] diet, which consists of oat flakes, dried milk powder and egg white, and were divided into eight groups for the administration of ascorbic acid. The doses were administered by mouth with a pipet from a solution of ascorbic acid freshly prepared daily, as follows:

| | |
|---|---|
| Group 1.....None | Group 5.....1.0 mg. daily |
| Group 2.....0.25 mg. daily | Group 6.....1.5 mg. daily |
| Group 3.....0.50 mg. daily | Group 7.....2.0 mg. daily |
| Group 4.....0.75 mg. daily | Group 8.....2.5 mg. daily |

All animals received in addition 0.50 cc. of cod liver oil twice weekly and were allowed free access to water. Studies of growth, maturity and nutritional status were made at three week intervals.

Those guinea pigs which received more than 1 mg. of ascorbic acid daily showed no gross evidences of disturbances in growth or maturity, although none was protected completely against scurvy, as judged by the criteria of Höjer [4] and Zilva and Wells.[5]

In all the groups which received less than 1 mg. of ascorbic acid daily there were significant disturbances in the progress in length and weight. Only those guinea pigs which survived more than fourteen weeks had their progress in maturity altered.

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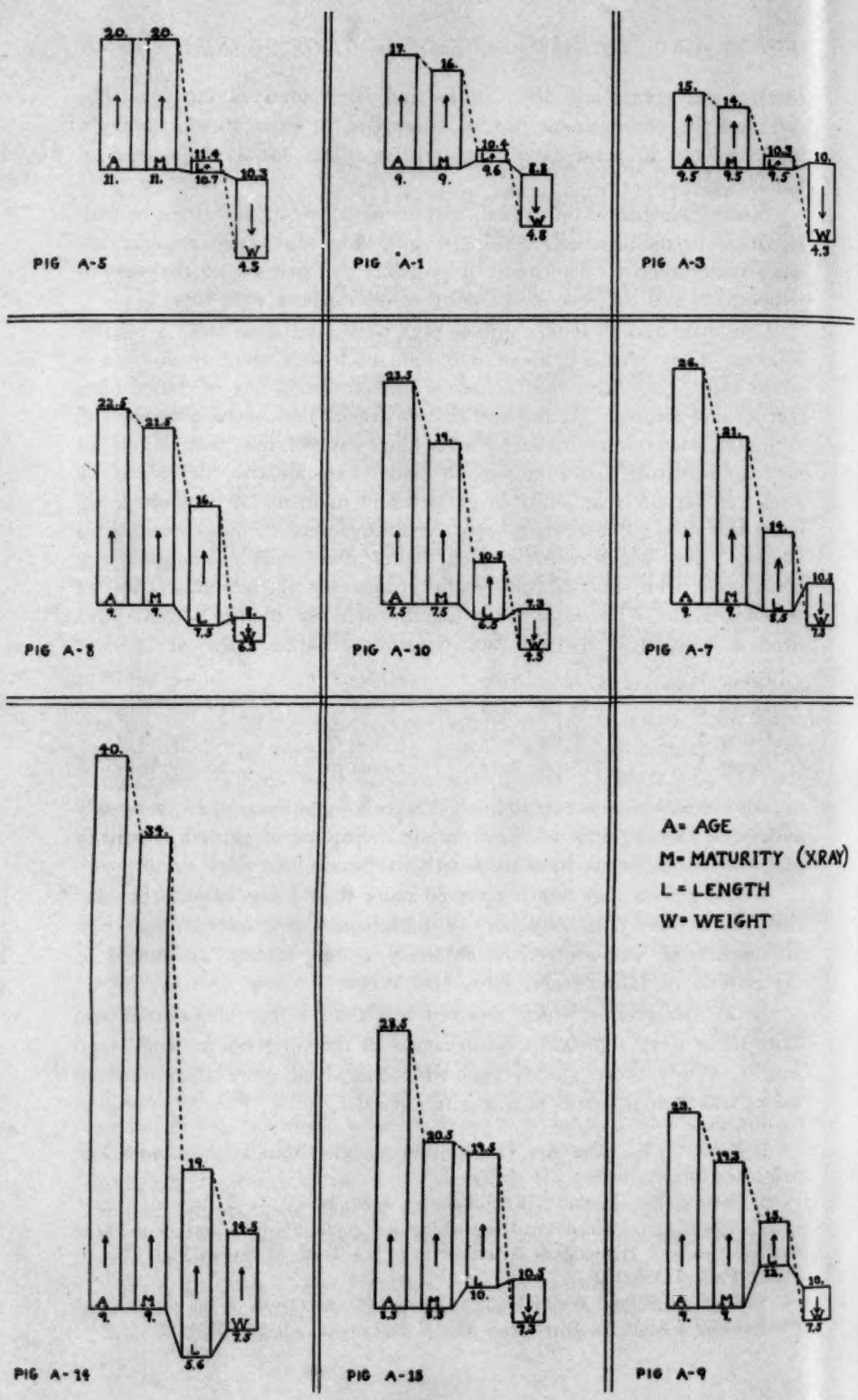
2. Zuck, T. T.: The Age Order of Epiphyseal Union in the Guinea Pig, Anat. Rec. **70**:389, 1938.

3. Demole, V.: Ztschr. f. Vitaminforsch. **3**:89, 1934.

4. Höjer, A.: Method for Determining the Antiscorbutic Value of a Foodstuff by Means of Histological Examination of the Teeth of Guinea-Pigs, Brit. J. Exper. Path. **7**:356, 1926.

5. Zilva, S. S., and Wells, F. M.: Changes in the Teeth of the Guinea Pig, Produced by a Scorbutic Diet, Proc. Roy. Soc., London, s.B **90**:505, 1917.




Disturbance of growth and development in the guinea pig.

Reference to the charts of guinea pigs A-3, A-1 and A-5, which lived five and a half, eight and nine weeks respectively, shows that these animals lost weight progressively from the beginning of the experiment and increased in length by less than one week's increment during the experiment. Despite the profound disturbance in growth all 3 animals continued to progress in maturity without significant alteration in rate.

Reference to charts of guinea pigs A-8, A-9, A-10, A-17 and A-15, animals which received a more liberal ration of ascorbic acid (0.50 mg. daily) and lived thirteen and a half, fourteen, sixteen, seventeen and twenty weeks respectively, shows a less profound loss of weight, larger increments in length and, after fourteen weeks, a lag in maturity.

The chart of guinea pig A-14, which received 0.75 mg. of ascorbic acid daily, shows that this animal gained in the thirty-one weeks it lived, the equivalent of a seven weeks' increment in weight, a thirteen weeks' increment in length and a twenty-five weeks' increment in maturity.

It is evident from these experiments that in malnutrition in the guinea pig associated with a deficiency of ascorbic acid progress in weight, length and maturity is interfered with. The interference is shown first in loss of weight or failure to make suitable gain in weight, next in failure to increase in length and finally in failure to achieve maturity. These observations are in accord with others, which will be published, which indicate that progress in weight, height and maturity in children follows the same general pattern as that reported for the guinea pig.

# Case Reports

## MESENTERIC VASCULAR OCCLUSION IN CHILDREN

### REPORT OF A CASE

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The first case of mesenteric vascular occlusion was reported by Tiedeman.[1] The disease was for a long time considered rare, but 214 cases were reported in 1904 by Jackson, Porter and Quinby.[2] Another series of 366 cases was reported in an excellent monograph on the subject by Trotter in 1913.[3] Other authors[4] have reported smaller series of cases. The lesion in adults is no longer regarded as uncommon.

The disorder is unusual in childhood and infancy.[5] Of the 308 patients in Trotter's series whose ages were noted, only 4 patients between the ages of 1 and 10 years could be found. The youngest of the 4 was 5 years old. Lagane[6] reported a case in a 1 month old infant. Frank[7] reported the condition in 3 children aged 8, 10 and 12 years, respectively. McClanahan[8] found the lesion in a 4 month old infant. Feldstein and Goldstein[9] reported its occurrence in a 6 year old girl. With the case to be added in this paper, only 11 cases in infants and children can be found in the English literature, although it is possible that a few have been overlooked inadvertently, because in many instances the age of the patient was not noted.

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From the Department of Pediatrics of the Spartanburg General Hospital.

1. Tiedeman, cited by Frank.[7]

2. Jackson, J. M.; Porter, C. A., and Quinby, W. C.: Mesenteric Embolism and Thrombosis: A Study of Two Hundred and Fourteen Cases, J. A. M. A. **42**:1469 (June 4) 1904; **43**:25-29 (July 2); 110-114 (July 9); 183-187 (July 16) 1904.

3. Trotter, L. B. C.: Embolism and Thrombosis of Mesenteric Vessels, London, Cambridge University Press, 1913.

4. Blackburn, J. H.: Mesenteric Thrombosis and Embolism: Report of Thirty-Five Cases, South. M. J. **9**:810-820, 1916.

5. Davison, W. C.: The Compleat Pediatrician, ed. 2, Durham, N. C., Duke University Press, 1938, p. 136.

6. Lagane, cited by Trotter.[3]

7. Frank, L.: Mesenteric Vascular Occlusion: Report of Three Cases in Children, Am. J. Surg. **37**:304-309, 1923.

8. McClanahan, V. B.: Mesenteric Thrombosis: Report of Case Four Months of Age, Illinois M. J. **49**:514-515, 1926.

9. Feldstein, G. J., and Goldstein, J. H.: Mesenteric Thrombosis, J. Pediat. **8**:720, 1936.

Males are affected almost twice as frequently as females. In one series [2] 64 per cent of the patients were men and 36 per cent women. In another series,[3] of the 316 patients whose sex was noted 193 were males and 123 females. The sex of the patient was indicated in only 5 of the reported occurrences of the disease in children. Four of the 5 patients were boys.

The symptoms of the disease are those of an acute abdominal condition. Clinical findings vary little, whether an artery or a vein is occluded singly or both together. The onset is usually sudden, with severe abdominal pain, which may continue, subside or become intermittent. Usually there is diarrhea at first, followed by constipation, which may become absolute. Constipation is due to intestinal atony associated with infarction. Distention with tenderness, and sometimes with rigidity, is present. The patient appears to be in a state of collapse, with rapid thready pulse, pale anxious facies and normal or subnormal temperature. Vomiting becomes almost continuous. In the later stages blood may be passed in the stools. The patient is usually comatose toward the end. Very rarely an abdominal tumor can be felt. Visible peristalsis was reported in only 4 of 366 cases.[3] It is readily seen that these signs and symptoms might point toward any one of a number of different acute abdominal conditions.

That mesenteric vascular occlusion is rarely diagnosed is shown by Trotter,[3] who found that of 366 cases only 13 had been correctly diagnosed prior to operation or autopsy.

The only treatment that offers any chance of recovery is early operation, if the condition of the patient permits. Technical details of the operation, naturally, will vary with the extent and portion of intestine involved as well as the surgeon's preference in methods of anastomosis. A patient treated medically rather than surgically is neglected; delay in operation may cost the patient his life.

The mortality depends on how soon the operation is performed, as well as on the extent and location of infarction and the condition of the patient. When no operation is performed the mortality is almost 100 per cent, although a few patients have lived when the collateral circulation was quickly established.[3] In the cases in which operation was performed Trotter [3] found that 36.2 per cent of the patients recovered. Perhaps refinements in technic have raised that proportion of recovery somewhat. At least, the chances of recovery with operation are poor, but without it the outlook is almost hopeless.

## REPORT OF CASE

H. M., one of white male twins, when admitted to the hospital on June 8, 1939, the day of birth, because of premature delivery weighed 4 pounds 8 ounces (2,040

Gm.). On July 21 the infant weighed 7 pounds 1½ ounces (3,217 Gm.), his best weight. His weight decreased and was only 5 pounds 15½ ounces (2,707 Gm.) on August 1, two days before his death. The temperature was normal until July 24, when it rose to 101.8 F. There was irregular fever after that until death. The Wassermann reactions of the infant's mother and twin brother were negative.

On July 28 a transfusion of 50 cc. of citrated blood was given. On July 30 the abdomen was greatly distended; the child was cyanotic and cried continuously from 7 a. m. There was no vomiting, but five stools, none of them bloody, were passed during the morning; the last one was small. Intussusception was suspected. In a surgical consultation it was decided that an operation was not indicated since there was no mass palpable in the abdomen after a stomach tube had relieved distention, and no rigidity. Two days later a fluoroscopic examination after a barium sulfate enema showed no filling defect; the lungs were clear, and a normal amount of air was present in the intestines. A blood count made the following day showed 17,200 white cells with a large percentage of polymorphonuclears. The patient did not eat well and had stools only after enemas. He continued the retracting of the head, begun some days previously, but no Kernig sign was present, and the degree of stiffness of the neck varied. He gave the impression of suffering from a ruptured appendix or abdominal infection of some kind. Next morning the patient's condition was worse. An attempt to aspirate pus from the abdomen by needle was unsuccessful. Even microscopic examination of a sample of physiologic solution of sodium chloride which had been infused into the abdomen and then withdrawn disclosed no pus and few red blood cells. At 10:55 a. m. the patient died, aged 56 days.

A postmortem examination was performed by Dr. E. B. Saye three and a half hours after death.

The thorax appeared normal. There was a small amount of blood-stained fluid in the peritoneal cavity. A section of the jejunum 25 cm. in length was dark red. The corresponding portion of the mesentery was similar in appearance, and some of the branches of the mesenteric vein contained red clots throughout. No band or torsion of the mesentery that might have caused the thrombosis was found; the mesenteric arteries in the involved region were normal. The anatomic diagnosis was: localized thrombosis of the mesenteric vein with extreme passive hyperemia of the jejunum.

## COMMENT

Prior to the onset of the acute abdominal condition, the infant had had mild diarrhea with four or five stools a day. His diet consisted of skimmed milk, calcium caseinate and water when the mesenteric occlusion occurred.

Mesenteric vascular occlusion was not even considered by any physician who saw this infant. The signs and symptoms were typical of intussusception, except for the absence of tumor and the passage of fecal material. Vomiting was not a predominating symptom, probably because a stomach tube was used to relieve distention and also because there was some movement of intestinal contents even in the presence of intestinal atony. Operation may not have saved this patient, but certainly his chances of recovery would have been enhanced.

Rare though it is in children, mesenteric vascular occlusion should be remembered when an acute abdominal condition is to be diagnosed.

SUMMARY

The symptoms, treatment and mortality of mesenteric vascular occlusion are discussed.

Reports of the occurrence of this lesion in infants and children are reviewed, and a new case in a 2 month old infant is presented.

# TENSE PNEUMOTHORAX IN AN INFANT

## SUCCESSFUL TREATMENT BY THE PRODUCTION OF CHEMICAL PLEURITIS

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PHILADELPHIA
AND
A. ALBERT CARABELLI, M.D.
TRENTON, N. J.

Cases of spontaneous pneumothorax are being reported with increasing frequency, due to a greater familiarity with the condition on the part of the medical profession as a whole and to the more frequent performance of roentgen examination. Such an examination is absolutely essential to clinch the diagnosis.

The condition, however, is still rarely reported in infants and children, especially the so-called valvular, or tense, pneumothorax. This is the type in which the intrapleural pressure remains above atmospheric pressure in both phases of quiet respiration. It is the result of a one way valve action through a rent in the visceral pleura. Forceful inspiratory effort, as in crying, pumps enough air into the pleural space to exert a positive pressure during the inspiratory phase of quiet breathing. This trapped air gradually reduces the vital capacity, which in turn stimulates greater respiratory effort, and a vicious circle results. The end effect of this positive pressure in one pleural space depends on the mobility of the mediastinum. If the mediastinum is rigid, effects of pressure are felt only on the involved side, and the contralateral lung can function normally and supply gas exchange adequate for quiet activity. If the mediastinum is mobile, however, the trapped air pushes it into the contralateral hemithorax, gradually compressing the healthy lung until the patient dies of suffocation.

This sequence of events explains the greater seriousness of the condition in infancy and childhood, when the mediastinum is in its normal, flexible condition. In adults the mediastinum is apt to be more or less rigid, so that while tense pneumothorax may cause considerable distress, when uncomplicated it is rarely the direct cause of death. Coccheri

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Read before the Philadelphia Pediatric Society, Jan. 9, 1940.

From the pulmonary clinic of the Graduate Hospital of the University of Pennsylvania.

and Rossi [1] reported 300 cases. Scott [2] surveyed 177 and Glaser and Landau [3] reported 17. Glaser and Landau stated: "Tension pneumothorax occurred five times, or in 30 per cent of the cases of our series, and was always fatal." Death is the usual termination of tense pneumothorax, although Strongin [4] reported 1 case with recovery.

In regard to the cause of the rent in the visceral pleura which results in spontaneous pneumothorax, cases fall naturally into three groups. In the first are those cases in which the pneumothorax is obviously due to direct trauma. In the newborn child this injury may be caused by the strenuous manipulations which are necessary to establish respiration, but in adults it is the result of some physical force applied to the visceral pleura. Damage may be caused by violence to the wall of the chest which is transmitted directly to the pleura, but it is more often the result of a tearing of adhesions, either with or without preexisting artificial pneumothorax. In the second group are those cases in which a necrotizing lesion in the lung has destroyed the continuity of the pleura before obliterative pleurisy has developed. In this group are the cases of spontaneous pneumothorax associated with a subpleural focus of tuberculosis, pulmonary abscess, pneumonia and bronchopneumonia, pulmonary gangrene or pulmonary infarction. The third group comprises cases in which the pneumothorax results from localized overinflation of the pulmonary parenchyma, which causes bursting of the alveoli and overlying pleura.

Ruge [5] has been credited with being the first to recognize that spontaneous pneumothorax is the result of a ball valve type of obstruction in a bronchus and that obstructive emphysema probably precedes pneumothorax. Hotz [6] has shown experimentally that when constantly increasing intra-alveolar tension results in spreading and finally rupture of the pulmonary tissue, the rupture occurs near the free knifelike margin of the lung. Macklin [7] has also shown experimentally that hyper-

1. Coccheri, P., and Rossi, V.: Il pneumotorace spontaneo nell'infanzia con speciale riguardo alla statistica eziologia, diagnosi clinica e radiologica, Arch. di pat. e clin. med. **11**:46, 1931.

2. Scott, A. J.: Spontaneous Pneumothorax in Children: Statistical Study of the Literature, with Case Reports, Tr. Sect. Dis. Child., A. M. A., 1928, p. 59.

3. Glaser, J., and Landau, D. B.: Pneumothorax of the Newborn, Am. J. Dis. Child. **50**:986 (Oct.) 1935.

4. Strongin, H.: Tension Pneumothorax in the Newborn: Report of Case with Recovery, Am. J. Dis. Child. **56**:110 (July) 1938.

5. Ruge, C.: Pneumothorax bie einem Neugeborenen, Ztschr. f. Geburtsh. u. Gynäk. **2**:31, 1878.

6. Hotz, A.: Ueber partiellen Spontanpneumothorax beim Neugeborenen, Schweiz. med. Wchnschr. **64**:209, 1934.

7. Macklin, C. C.: Transport of Air Along Sheaths of Pulmonary Blood Vessels from Alveoli to Mediastinum: Clinical Implications, Arch. Int. Med. **64**: 913 (Nov.) 1939.

inflation of a portion of the lung results in rupture of alveoli into the interstitial tissue and, secondarily, through the pleura. It remained for Silver [8] to present a case in which roentgen examination proved that a stage of obstructive emphysema preceded the bursting of the pleura and the development of pneumothorax.

It is worthy of note that in the first two of the groups of cases discussed the valve action is at the pleura itself, whereas in the third group the check valve may be situated deep in the lung in a bronchus the walls of which are reenforced by cartilage and are, therefore, resistant to the compression which would convert the check valve into complete obstruction.

In the treatment of spontaneous pneumothorax efforts are directed primarily at bringing about a closure of the pleural rent. Closure will occur spontaneously in a large number of cases, coincident with the collapse of the lung, and no further treatment is necessary. In fact, nature should be allowed to act without interference, except for those cases in which the pneumothorax persists or recurs or in which a positive pressure develops. In them simple withdrawal of air may be sufficient, or a period of continuous water-sealed aspiration may be necessary. There are certain cases, however, in which the persistence or recurrence of tense pneumothorax creates an urgent need for more energetic measures. It is a long-standing clinical observation that the spontaneous development of a pleural effusion, however small, usually results in closing of the pleural rent. It was this observation that led to the suggestion of purposefully causing a pleural reaction with effusion.

Recently Hennell and Steinberg [9] reviewed 12 cases they collected from the literature and added 5 of their own in which the production of chemical pleuritis resulted in the closure of rents in the pleura. They stated that Spengler was the first to suggest such a procedure, in 1901. Solutions of dextrose in various strengths have most frequently been used for this purpose, although a variety of other substances, such as 1 per cent solution of silver nitrate, oil of turpentine, venous blood, guaiacol, iodoform and iodized oil, has also been successfully used. All of Hennel and Steinberg's patients were adults or older children, the youngest being 5 years of age.

The following case has some unusual features of sufficient interest to be placed on record. The patient was an infant, the condition was recurrent, and each recurrence was accompanied by high intrapleural pressure; cure was accomplished by the production of chemical pleuritis.

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8. Silver, H. B.: Spontaneous Pneumothorax in a Newborn: Report of Case in Which Mechanism Was Demonstrated, Am. J. Dis. Child. **57**:907 (April) 1939.

9. Hennell, H., and Steinberg, M. S.: Tense Pneumothorax: Treatment of Chronic and Recurrent Forms by Induction of Chemical Pleuritis, Arch. Int. Med. **63**:648 (April) 1939.

REPORT OF A CASE

Baby Jones was the first-born child of nontuberculous parents. He was born on June 28, 1938. The presentation was cephalovertex, right occipitoanterior position. Labor was not unduly prolonged, and delivery was accomplished by the use of low forceps with the mother under ether anesthesia. The child required a few minutes of artificial respiration before normal breathing began; no mention was made of any respiratory distress or cyanosis. At birth the weight was 7¼ pounds (3,288 Gm.), and on the date of discharge, ten days later, it was 7 pounds 6 ounces (3,345 Gm.). On discharge the child appeared to be healthy and perfectly normal.

On October 3 the child was admitted to the pediatric service of the St. Francis Hospital with a history of severe dyspnea and cyanosis, which had begun two days previously and which had become progressively worse. On admission no crying or apparent pain was noticed, and the child was fairly comfortable and took nourishment well. Examination revealed a rather pale, frail infant who gasped for breath on occasion but was not very cyanotic. There were physical signs of pneumothorax on the left side, although some breath sounds were audible anteriorly at the base of the left lung. The percussion note over the left side of the chest had a markedly tympanitic note. A roentgenogram taken at this time (fig. 1 *A*) showed a large pneumothorax in the left side of the chest with adhesions binding the lung to the lower part of the wall of the chest and to the diaphragm. There was a tremendous shift of the mediastinal structures to the right; the heart was pushed almost against the right wall of the chest.

Conservative treatment did not help, and the pneumothorax showed no evidence of decreasing; as a matter of fact, the child became progressively more dyspneic and cyanotic until he could barely breathe. His respirations became short and gasping, with periods of apnea during which cyanosis increased tremendously. The diagnosis at this time was valvular pneumothorax with a large rent in the lung. The desperate condition of the child forced us to attempt decompression of the tense pneumothorax. On October 9 a needle was introduced into the pleural space and attached to a water manometer; the puncture was made in the fourth intercostal space, on the anterior axillary line. The pressure of the air in the pleural space was so great that it blew the water from the manometer with considerable force, although the instrument is one which records a pressure of + 20 cm. After an undetermined amount of air had escaped, the manometer was again attached to the needle, and the readings of pressure obtained were + 10 cm. of water on expiration and + 6 cm. on inspiration. Four hundred cubic centimeters of air was removed under controlled aspiration, and the final manometric readings were 0 and — 4 cm. of water on expiration and inspiration, respectively. In the interim the child underwent apparent resuscitation; breathing became normal, and cyanosis completely disappeared. In a few minutes, however, a strongly positive pressure within the pleural cavity was built up, and the child again suffered from gradual asphyxia. This sequence of events left no doubt in our minds as to the valvular character of the pulmonary rent.

The insertion of a needle was all that was needed to restore normal pressure, but our problem was to decide on a course which would lead to permanent decompression of the space. We thought of underwater decompression, but with such a restless child this method was not practical. We finally decided that if we could introduce a Sise needle guard (for want of a better apparatus in this emergency) into the space, we could keep the pressure at atmospheric level, for the guard could act as a safety vent to prevent increase in pressure. Therefore the guard

was introduced, covered with a sterile dressing and strapped firmly to the chest. By this method the child was kept fairly comfortable; the breathing was more or less natural, and cyanosis completely disappeared. A roentgenogram (fig. 1*B*) taken at this time showed considerable reexpansion.

On October 11 the needle guard worked loose; the end was found to be in the soft tissue of the wall of the chest, plugged with coagulum. The child at this

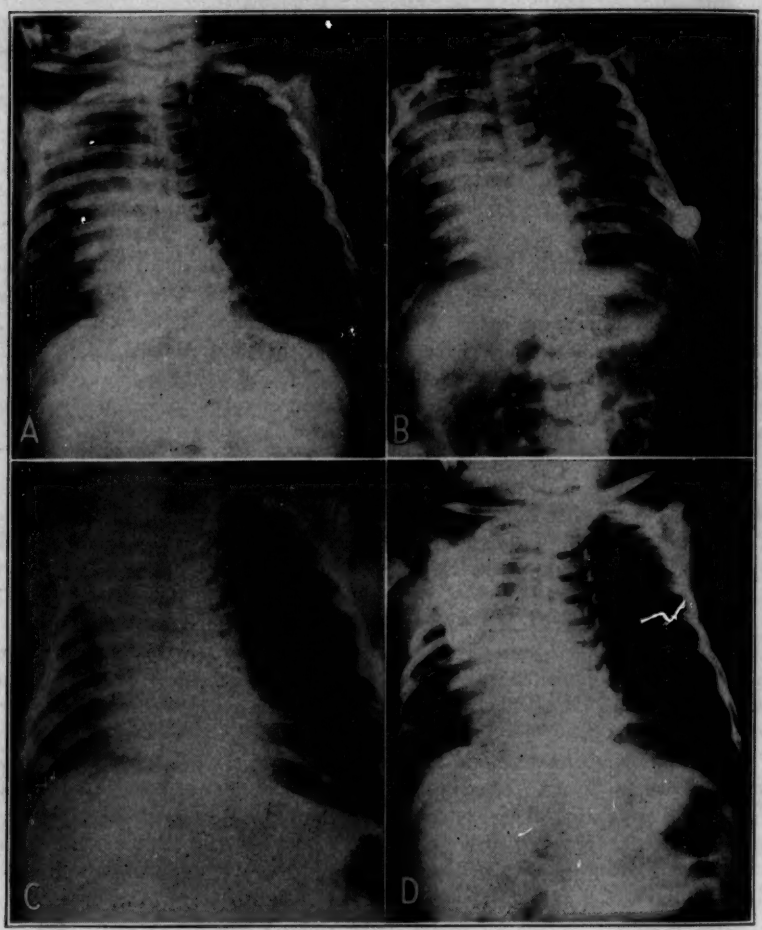


Fig. 1.—*A*, roentgenogram taken on first admission of the patient to the hospital, showing large pneumothorax in the left side of the chest with adhesions binding the lung to the lower part of the wall of the chest and to the diaphragm. *B*, roentgenogram taken after insertion of Sise needle guard, showing the considerable reexpansion of the left lung. *C*, roentgenogram taken after the needle guard worked loose and was removed, showing a greater degree of pneumothorax than in figure 2 but less than in figure 1. *D*, roentgenogram taken on the patient's second admission to the hospital, showing a condition similar to that on the first admission.

time was comfortable, and the guard was left out in the hope that closure of the pleural tear would follow spontaneously. Roentgen examination (fig. 1 *C*) showed a greater degree of pneumothorax than with the needle in place but less evidence of pressure than at first. On October 16, at the insistence of the parents, the child was discharged, in apparently good condition.

The second admission was on October 24, with much the same complaints and clinical picture as the first time, except that now there was marked dyspnea

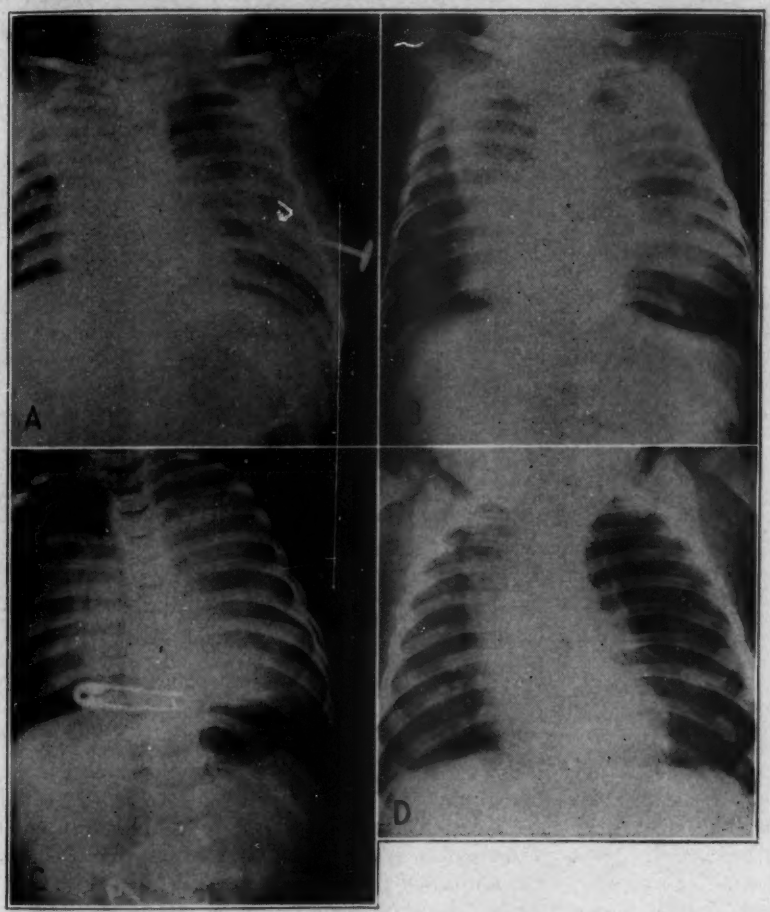


Fig. 2.—*A*, roentgenogram taken after the pleuritis reaction to the instillation of 12 cc. of a 50 per cent solution of dextrose had subsided, showing marked reexpansion of the left lung. *B*, roentgenogram taken twelve days after instillation of the solution of dextrose, showing pneumonia in the upper lobe of the left lung. *C*, roentgenogram taken after the pneumonia subsided, showing empyema pointing in the axillary region of the left side of the chest. *D*, roentgenogram taken about fourteen months after symptoms of pneumothorax first developed, showing that the left lung is completely reexpanded and that the heart is only slightly displaced to the right.

and cyanosis from the onset. This return of symptoms followed what appeared to be a mild infection of the upper respiratory tract, which the child had acquired a few days previously. The roentgenogram (fig. 1 *D*) was similar to that taken at the first admission.

Once more the needle guard was inserted to prevent asphyxia, and once more the pressure was so high that it blew the water from the manometer. On this occasion the needle guard had to be kept in constantly, and when it worked out or became plugged with coagulum, as it did on several occasions, it had to be immediately reinserted to prevent death.

This case was presented as an interesting therapeutic problem at the conference on diseases of the chest of the Graduate Hospital of the University of Pennsylvania, and several possible methods of treatment were discussed. The use of an irritating solution to produce pleural effusion seemed the most simple and feasible therapy in a child of this age, and a 50 per cent solution of dextrose was the substance chosen to produce chemical pleuritis.

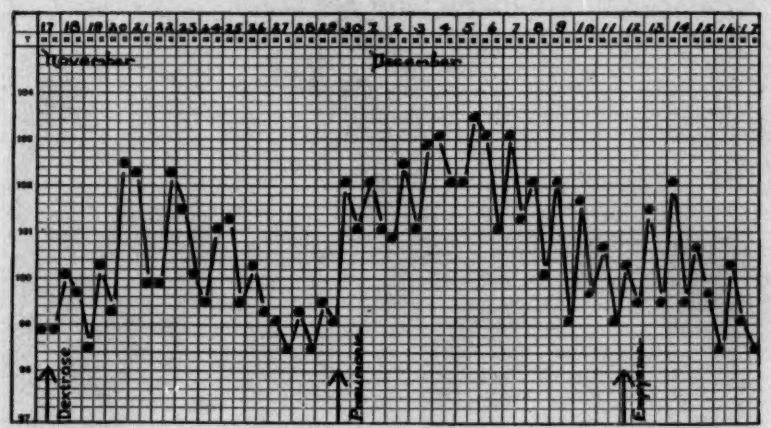


Fig. 3.—Chart of the temperature readings during a month of the second stay in the hospital.

On November 18, 12 cc. of a 50 per cent solution of dextrose was introduced into the pleural cavity through the Sise guard, which had been in place for the preceding three weeks. This quantity was chosen arbitrarily, as we had no idea of the amount to use. No immediate symptoms followed its introduction into the space. Two days after the instillation the temperature began to rise, reaching a peak of 102.4 F., and returned slowly to normal in seven days. We considered that this reaction indicated chemical pleuritis. Some effusion was created, but this was blown out through the needle guard, and there was marked reexpansion of the lung (fig. 2 *A*). The temperature stayed normal for three days, when there was an abrupt rise to 103 F., and there developed all the classic signs and symptoms of pneumonia of the upper lobe of the left lung, which had apparently completely reexpanded. When the pneumonia was discovered (fig. 2 *B*), the guard was removed (twelve days after the instillation of the dextrose). The pneumonia subsided by lysis, and the temperature had almost reached normal when it again began to rise. It was not sustained as previously, however, and soon was of the septic type. After seven days of this type of temperature an empyema of the left

side of the chest was discovered to be pointing in the axilla (fig. 2 *C*). This was drained by the intercostal method. The tube was removed on the seventh day, and complete healing of the wound resulted in several more days. All these occurrences can be followed graphically on the temperature chart (fig. 3).

Up to the time of writing this report, December 1939, this child had been under constant clinical and roentgenographic observation and had had no recurrences. The breath sounds on both sides were of about equal intensity, and the mediastinal structures were gradually assuming their normal relation. The last fluoroscopic examination revealed the heart displaced only slightly to the right; this position was confirmed by roentgen examination (fig. 2 *D*). The weight of the child was normal for his age and height.

In the differential diagnosis the possibility of a valvular pneumocyst was considered and could not be disproved, but the subsequent course, with development of pneumonia in the upper lobe of the left lung, which was previously compressed, left no doubts in our minds that a diagnosis of tension pneumothorax was warranted.

SUMMARY

The etiology, classification and treatment of tense pneumothorax is briefly discussed.

A case is presented in detail of recurrent tense pneumothorax in an infant, which was successfully treated by induction of chemical pleuritis with a 50 per cent solution of dextrose.

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# METHEMOGLOBINEMIA OF UNKNOWN ORIGIN IN A TWO WEEK OLD INFANT

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Methemoglobinemia not caused by drugs or exogenous poisons is a relatively rare condition. A case of "idiopathic" methemoglobinemia in a 2 week old infant is presented in which prompt disappearance of cyanosis followed the intravenous administration of methylthionine chloride U. S. P. (methylene blue).

## REPORT OF A CASE

B. J. T., a 2 week old white girl, was referred to the St. Louis Children's Hospital from Farber, Mo., on Feb. 15, 1939, because of cyanosis first noted a week before admittance. The family history revealed the parents and 1 sibling living and well. The mother, who had been in good health during the pregnancy, affirmed that she had taken no medicine of any nature for at least three months before the birth of the baby. No relative was known to have suffered from prolonged or intermittent cyanosis.

The patient, weighing about 3,500 Gm., was born at home after an easy labor of seven hours during which no anesthetic, sedative or instrument was used. The cry was spontaneous, and there was no respiratory or circulatory distress. As the mother had an inadequate supply of breast milk, the patient was given a formula made up of evaporated milk, water and corn syrup (Karo). The child took its feedings well and seemed entirely normal until the onset of the present illness.

On February 9 the parents observed that the patient had become deeply cyanotic. The child showed no restlessness or respiratory difficulty. She continued to take her feedings normally. The family physician tentatively diagnosed congenital heart disease. No medicine was prescribed, and repeated questioning revealed that none had been given at any time before or after the onset of the illness. A little whisky had been administered on the first day of the disease. During the following three days, although the color appeared improved, the cyanosis was still prominent when the baby cried. The infant's appearance was said to have been perfectly normal during the subsequent two days, but on February 15 the cyanosis reappeared. It rapidly became so intense that the child was thought to be dying and was rushed to the hospital.

Examination in the admitting room showed a normally developed female infant weighing 3,500 Gm., whose skin and mucous membranes showed a remarkable, deep, slate gray cyanosis which became more pronounced with crying. The temperature was

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37 C. (98.6 F.). The respirations were neither increased nor labored. The hydration was excellent. The eyes, ears, nose and throat were normal. No nuchal rigidity was elicited. The lungs were clear to percussion and auscultation. The size of the heart was normal, and its sounds were of good quality unaccompanied by murmurs. Abdominal examination showed no distention or visceral enlargement. The genitalia and the extremities were normal.

Fluoroscopic examination showed a widened mediastinal shadow in the supracardiac area which was interpreted from a subsequent roentgen film as an enlarged thymus. The heart was not enlarged. An electrocardiogram showed a normal tracing. Examination of the blood showed 4,360,000 red blood cells, with 14 Gm. of hemoglobin (Newcomer), and 30,000 white blood cells. The differential count revealed 18 per cent neutrophilic stab forms, 40 per cent polymorphonuclears, 36 per cent lymphocytes and 6 per cent monocytes.

The patient was immediately placed in an oxygen tent, but there was no improvement in her color. The administration of coramine (a 25 per cent solution of pyridine betacarbonic acid diethylamine) was likewise ineffective. Shortly after her admittance the patient was seen by Dr. A. F. Hartmann, who suggested that the unusual cyanosis resembled that seen in methemoglobinemia accompanying the administration of the sulfonamide derivatives. Accordingly a specimen of the infant's blood was examined spectroscopically. The presence of methemoglobin was at once established, and a quantitative estimate made by the method of Wendel [1] revealed that 57 per cent of the total pigment had been changed to this form. Examination of the blood for sulfanilamide and its derivatives [2] gave negative results.

One cubic centimeter of a 1 per cent solution of methylthionine chloride (approximately 3 mg. per kilogram of body weight) was then given intravenously. In one-half hour the cyanosis had completely disappeared. This change was dramatically recorded in colored motion pictures taken before and after treatment. Reexamination of the blood two hours after injection of the dye showed no trace of methemoglobin.

A close check of the spectroscopic determination of the amount of methemoglobin present before treatment was obtained when the oxygen capacity of the blood at that time was found to be 9.9 volumes per cent, equivalent to 7.4 Gm. of hemoglobin.[3] After treatment, the oxygen-carrying capacity of the blood was 19.8 volumes per cent, the equivalent of 14.8 Gm. of hemoglobin, indicating that the amount of nonfunctioning hemoglobin (methemoglobin) had been 14.8 Gm. less 7.4 Gm., or 7.4 Gm. (50 per cent of total). The previous calculation by the direct spectroscopic method revealed 57 per cent of the total pigment was methemoglobin.

The total pigment of the blood determined by the acid hematin method of Newcomer was 14 Gm. before treatment and 13.9 Gm. after treatment, both values

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1. Wendel, W. B.: Methemoglobin Determination: A Clinical Method, J. Lab. & Clin. Med. **24**:96 (Oct.) 1938.

2. Marshall, E. K., Jr.: Determination of Sulfanilamide in Blood and Urine, Proc. Soc. Exper. Biol. & Med. **36**:422 (April) 1937.

3. Using Hüfner's factor (1 Gm. of hemoglobin carries 1.34 volumes per cent of oxygen at 0 C. and 760 mm.), 9.9 divided by 1.34 equals 7.4 (Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931, vol. 1, p. 524).

approximating closely the more accurate 14.8 Gm. calculated from the oxygen-combining capacity of the hemoglobin.[4]

The patient was detained in the hospital ten days after admittance, but no recurrence of the methemoglobinemia was detected. During that time there was no evidence of disease. The infant passed two to three stools daily which were normal in color and consistency. No culture for the nitroso bacillus was made. Spectroscopic examination of the blood a week after discharge failed to show any trace of abnormal pigment. A month later the family reported that the patient's color had remained normal. Further follow-up study showed that the infant developed normally (sat at 5 months, cut teeth at 6 months and crawled at 7 months). Close observation by the family physician for eight months after the illness revealed no recurrence of the cyanosis. Analysis of a can of evaporated milk of the same brand and purchased at the same time as that given to the patient failed to show any trace of sulfanilamide which could conceivably have been excreted in the milk of cows given the drug for the treatment of mastitis.

## COMMENT

Since the universal employment of the sulfonamide compounds in the treatment of acute bacterial infections, the recognition of methemoglobinemia has become commonplace. Previous to Domagk's[5] discovery in 1935 of the therapeutic effectiveness of sulfanilamide, methemoglobinemia was a relatively uncommon disease found principally in industrial workers exposed to coal tar derivatives, such as aniline, nitrobenzene and the nitrophenols. This condition has also been described in patients who have taken excessive amounts of various drugs, especially bismuth subnitrate or acetanilid or proprietary remedies containing these substances. Methemoglobinemia also occurs in potassium chlorate poisoning.

Methemoglobinemia has been reported in a variety of conditions other than those caused by drugs and exogenous poisons. According to van Lier[6] the pigment is found in the blood of some patients with

4. P. H. Long and E. A. Bliss (The Clinical Use of Sulfanilamide, Sulfapyridine and Allied Compounds, New York, The Macmillan Company, 1939, p. 271), quoting from Peters and Van Slyke (cited in footnote 3, vol. 2, p. 663), commented on the unreliability of the acid hematin methods of Sahli and Newcomer for the determination of total pigment values in the presence of methemoglobin. Wendel,[11] investigating the sources of this opinion (Wu, H.: Studies on Hemoglobin: I. The Advantage of Alkaline Solutions for Colorimetric Determination of Hemoglobin, J. Biochem. **2**:173 [Oct.] 1923. Stadie, W. C.: A Method for the Determination of Hemoglobin in Blood, J. Biol. Chem. **41**:237 [Feb.] 1920), found that the use of excessive amounts of ferricyanide for the production of methemoglobin probably accounted for the inaccuracy of the readings. Wendel's experiments showed that the Newcomer procedure gave correct total pigment values on blood containing methemoglobin produced by nitrite.

5. Domagk, G.: Ein Beitrag zur Chemotherapie der bakteriellen Infectionen, Deutsche med. Wchnschr. **61**:250 (Feb.) 1935.

6. van Lier, H. W.: Over de Parhaemoglobinaemieën, Utrecht, 1933; cited by Bensley, Rhea and Mills.[10]

eclampsia, blackwater fever,[7] hemolytic icterus, paroxysmal hemoglobinuria and infection by anaerobic bacteria. In those conditions caused by hemolysis, methemoglobin is said to be found in the plasma and not in the red blood corpuscles.

Spontaneous methemoglobinemia is a rare disease. It was first described by Stokvis [8] and Talma [9] in 1902, but as these writers failed to distinguish between sulfhemoglobin and methemoglobin [10] the accuracy of their observations is open to question. Van den Bergh [11] in 1905 reported 2 cases of peculiar cyanosis, in 1 of which the condition was due to methemoglobinemia and in the other, to sulfhemoglobinemia. Since that time there have been described under the name of "enterogenous cyanosis" [12] a number of similar cases in which the condition was caused by either methemoglobin or sulfhemoglobin. Having in common a peculiar cyanosis, these cases of sulfhemoglobinemia and methemoglobinemia differ in their clinical history in that the former are usually associated with severe headache and chronic constipation while the latter show exacerbations of cyanosis with attacks of profuse diarrhea and abdominal pain. In both conditions treatment has been of but temporary value in the great majority of patients, and the cyanosis persists intermittently for years. It is of interest that Waterfield [13] and Henstell and Dameshek [14] have each described a case in which both pigments were found in the blood at the same time.

The causation of these abnormalities of pigment metabolism associated with gastrointestinal symptoms is not known. It has been sug-

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7. H. Foy and A. Kondi (Spectrographic Analysis of Pigments in Serum and Urine of Blackwater Fever, Tr. Roy. Soc. Trop. Med. & Hyg. **32**:49 [June] 1938), in their studies of blackwater fever in Greece, were unable to confirm the finding of true methemoglobinemia.

8. Stokvis, B. J.: Zur Casuistik der autotoxischen enterogenen Cyanosen, Internat. Beitr. z. inn. Med. **1**:597, 1902.

9. Talma, S.: Intraglobulare Methämoglobinämie beim Menschen, Berl. klin. Wchnschr. **39**:865, 1902.

10. Sulfhemoglobin and methemoglobin have been confused because of the similarity of the absorption bands on spectroscopic examination. The pigments are easily distinguishable, however, as the addition of sodium cyanide or ammonium sulfide results in the rapid disappearance of the methemoglobin, while the more stable sulfhemoglobin remains unchanged.

11. van den Bergh, A. A. H.: Enterogene Cyanose, Deutsches Arch. f. klin. Med. **83**:86 (May) 1905.

12. "Enterogenous cyanosis" is a term which has been largely abandoned, as it fails to distinguish between methemoglobinemia and sulfhemoglobinemia.

13. Waterfield, R. L.: The Alternation and Subsequent Combination of Met- and Sulph-Haemoglobinaemia in One Patient, Guy's Hosp. Rep. **78**:265 (July) 1928.

14. Henstell, H. H., and Dameshek, W.: Enterogenous Cyanosis with Met- and Sulfhemoglobinemia: Clinical and Spectrophotometric Studies, J. Clin. Investigation **15**:464 (May) 1936.

gested that methemoglobinemia and sulfhemoglobinemia in these cases result from undue absorption of nitrites from the saliva [15] and from the gastrointestinal tract.[16] In the presence of hydrogen sulfide sulfhemoglobin rather than methemoglobin is thought to be formed. A nitrite-producing bacillus, recovered from the stool or sputum in a few instances of sulfhemoglobinemia, is believed to be the source of the excessive nitrite.[17] These findings have not been confirmed by most workers in their studies of both types of pigment abnormality.[18]

Bensley, Rhea and Mills,[19] describing 2 patients with familial idiopathic methemoglobinemia, could find in the literature but 5 other cases in which the condition was unassociated with drugs, systemic disease or severe gastrointestinal disturbances. In all but 1 of these cases the disease dated from birth. The cyanosis was constant and unaffected by treatment. Bensley and his co-workers discovered the condition in a brother and sister, 37 and 43 years of age respectively, in each of whom the cyanosis had not been noted before the age of 11 years. No etiologic factor could be discovered.

We have been unable to find a satisfactory explanation for the methemoglobinemia of the patient described in this report. The possibility of drug administration is unlikely in view of the history, which is felt to be reliable. Examination of the milk fed to the infant revealed no sulfanilamide. Study of the patient's blood for the sulfonamide derivatives by diazotization according to the method of Marshall [2] showed a barely discernible pink color which was not found in a number of similarly treated normal bloods. At this hospital, as we have never found large amounts of methemoglobin in patients treated with sulfanilamide or sulfapyridine without simultaneously finding appreciable levels of these drugs in the blood, we do not believe that this faint color could have represented the presence of traces of these dyes. We are unable to explain the development of this color change. Tests for

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15. Wallis, R. L. M.: On Sulphaemoglobinemia, Quart. J. Med. **7**:73 (Oct.) 1913.

16. van den Bergh, A. A. H., and Gutterink, A.: Enterogene Cyanose, Berl. klin. Wchnschr. **43**:7, 1906. Lichtenbelt, J. W. T.: Intraglobular Methemoglobinemia, Geneesk. gids **1**:545, 1923; cited by Bensley, Rhea and Mills.[19]

17. Garrod, L. P.: On Sulphaemoglobinaemia, Quart. J. Med. **19**:86 (Oct.) 1925. Wallis.[15]

18. Long, W. C., and Spriggs, E. I.: On Sulphaemoglobinaemia, Quart. J. Med. **11**:102 (Jan.) 1918. Mason, V. R., and Conroy, F. D.: Sulphaemoglobinaemia, Bull. Johns Hopkins Hosp. **32**:391 (Dec.) 1921. Parsons, L. G.: Goulstonian Lectures: On Some Wasting Disorders of Early Infancy, Lancet **1**:939 (May 10) 1924. Miller, R.: A Case of Enterogenous Methaemoglobinemia (?Congenital) in a Child, Arch. Dis. Childhood **5**:73 (Feb.) 1930. Dieckmann, W. J.: Methemoglobinemia, Arch. Int. Med. **50**:574 (Oct.) 1932.

19. Bensley, E. H.; Rhea, L. J., and Mills, E. S.: Familial Idiopathic Methemoglobinemia, Quart. J. Med. **7**:325 (April) 1938.

nitrites in the blood were unfortunately not performed. There was no constipation, diarrhea or abdominal pain, symptoms which have been described in some cases of methemoglobinemia. The patient showed no evidence of any systemic disease. This case is also probably to be excluded from the small group of previously described cases of congenital methemoglobinemia, since in all these cases the cyanosis persisted for years. It is conceivable, however, that our patient may fall into the latter group by showing the characteristic cyanosis later in life. It is noteworthy that the cyanosis in the cases reported by Bensley and his co-workers [19] was not observed until the patients were 11 years of age.

In 1933 Williams and Challis [20] and Steele and Spink [21] independently reported the successful use of methylthionine chloride in the treatment of methemoglobinemia associated with poisoning by coal tar derivatives. The former observers recorded the disappearance of the cyanosis within an hour after intravenous administration of the dye, while the latter workers demonstrated even more rapid improvement in the color of their patients. Hauschild,[22] in 1936 and 1937, using both thionine and methylthionine chloride in the treatment of experimentally produced methemoglobinemia, demonstrated that when the methemoglobin levels have risen to from 40 to 50 per cent of the total pigment, practically all of the abnormal pigment can be reconverted to hemoglobin, often within ten minutes. He also showed that the use of thionine prophylactically is effective in checking the formation of methemoglobin. Following the suggestion of Wendel [23] in 1937 that methylthionine chloride be used to relieve the methemoglobinemia caused by sulfanilamide, several investigators [24] have conclusively demonstrated the efficacy of this agent. Hartmann, Perley and Barnett [24a] have found the oral administration of methylthionine chloride satisfactory in most cases. When great excesses of methemoglobin have accumulated or

20. Williams, J. R., and Challis, F. E.: Methylene Blue as an Antidote for Aniline Dye Poisoning, J. Lab. & Clin. Med. **19**:166 (Nov.) 1933.

21. Steele, C. W., and Spink, W. W.: Methylene Blue in the Treatment of Poisoning Associated with Methemoglobin, New England J. Med. **208**:1152 (June 1) 1933.

22. Hauschild, F.: Untersuchungen über die Wirkung einiger Redoxyfarbstoffe bei Zuständen gestörter Atmung: I. Katalysin (Thionin) und Methämoglobinvergiftung, Arch. f. exper. Path. u. Pharmakol. **182**:118, 1936; Die Wirkung des Katalysins (Thionin) bei der Methämoglobinvergiftung, ibid. **184**:458, 1937.

23. Wendel, W. B.: Use of Methylene Blue in Methemoglobinemia from Sulfanilamide Poisoning, J. A. M. A. **109**:1216 (Oct. 9) 1937.

24. (*a*) Hartmann, A. F.; Perley, A. M., and Barnett, H. L.: A Study of Some of the Physiological Effects of Sulfanilamide: II. Methemoglobin Formation and Its Control, J. Clin. Investigation **17**:699 (Nov.) 1938. (*b*) Wendel, W. B.: The Control of Methemoglobinemia with Methylene Blue, ibid. **18**:179 (March) 1939. (*c*) Campbell, D., and Morgan, T. N.: Cyanosis Caused by Sulfonamide Compounds, Lancet **2**:123 (July 15) 1939.

when rapid removal of this pigment is desirable, as is the case before a major surgical procedure, the intravenous route is recommended.

Acting as a catalytic agent, methylthionine chloride has been shown to oxidize hemoglobin to methemoglobin with the subsequent reoxidation of the reduced (leuko) methylthionine chloride by reaction with oxygen.[25] This phenomenon has been employed in the treatment of cyanide poisoning, as methemoglobin rapidly binds cyanide to the nontoxic cyanmethemoglobin. On the other hand, the manner in which methylthionine chloride acts to reduce methemoglobin to hemoglobin is unknown. Wendel [24b] suggested that the leuko methylthionine chloride is probably formed in the actively metabolizing body tissues and is then returned to the red cells to be reoxidized to methylthionine chloride as it reduces the trivalent iron of methemoglobin to the bivalent iron of hemoglobin.

The prompt and complete disappearance of methemoglobin in the patient described in this paper is typical of the therapeutic results with methylthionine chloride obtained in the treatment of other patients at this hospital. The percentage of hemoglobin found as methemoglobin was remarkably high, no comparable levels having been determined in the patients treated here with sulfanilamide or associated compounds. It is a common observation that the color of patients with moderate degrees of cyanosis due to methemoglobin will become normal within one to three days after the causative agent has been withdrawn. In patients with severe cardiac or pulmonary disease, however, the value of changing promptly even moderate amounts of nonfunctioning hemoglobin to hemoglobin capable of transporting oxygen cannot be questioned.

It has not been demonstrated that methemoglobin is toxic except so far as its formation reduces the oxygen-combining capacity of the blood. Dennig [26] found that death ensued in dogs when two thirds of the hemoglobin had been converted to methemoglobin. Instances of fatalities due largely to methemoglobinemia are recorded in the literature. Roe,[27] reporting a death in an infant associated with intense cyanosis due to methemoglobin following the administration of bismuth subnitrate, also cited 2 similar cases described previously. Although our patient did not seem to be in immediate danger of death, the high percentage of methemoglobin in the blood made her condition potentially precarious. Treatment with methylthionine chloride rapidly and completely removed this danger.

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25. Warburg, O.; Kubowitz, F., and Christian, W.: Ueber die katalytische Wirkung von Methylenblau in lebenden Zellen, Biochem. Ztschr. **227**:245, 1930.

26. Dennig, A.: Ueber die Einwirkung einiger vielgebrauchter Arzneimittel auf die Methämoglobinbildung in Blute, Deutsches Arch. f. klin. Med. **65**:524 (Feb.) 1900.

27. Roe, H. E.: Methemoglobinemia Following the Administration of Bismuth Subnitrate, J. A. M. A. **101**:352 (July 29) 1933.

SUMMARY

A unique case of methemoglobinemia of unknown cause in a 2 week old infant is presented. The use of methylthionine chloride intravenously resulted in prompt disappearance of the cyanosis. Methemoglobinemia as previously described in the literature is briefly discussed. The effectiveness of methylthionine chloride in the therapy of this condition is noted.

# ARACHNODACTYLY (MARFAN'S SYNDROME) WITH SEVERE ANEMIA

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The condition characterized by elongation and narrowness of the long bones, particularly those of the metacarpals, fingers and toes, was named *dolichostenomélie* (long narrow limbs)) by Marfan in 1896.[1] It is now more generally called arachnodactyly (spider fingers), a term first used by Achard in 1902.[2] About 200 cases have been reported to date.[3] Several observers [4] have found a definite familial incidence in arachnodactyly. The condition is important chiefly because of serious lesions that accompany the bony abnormality. As is mentioned by Lloyd [4a] and Burch,[4c] dislocation of the lenses of the eyes occurs in at least half of the cases. Spinal curvature was reported first by Méry and Babonneix [5] and is usually present,[4a] being found especially as kyphosclerosis. These spinal deformities are generally attributed to muscular weakness rather than to bony deformity. Piper and Irvine-Jones [6] stated that congenital disease of the heart was frequently present in cases of arachnodactyly. In cases reported by Dubois [7] and by Norcross [4e] there was congenital dislocation of the hip.

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From the Department of Pathology, Cornell University Medical College, and the New York Hospital.

1. Marfan, A. B.: Bull. et mém. Soc. méd. d. hôp. de Paris **13**:220, 1896.

2. Achard, C.: Bull. et mém. Soc. méd. d. hôp. de Paris **19**:834, 1902.

3. Futcher, P. H., and Southworth, H.: Arachnodactyly and Its Medical Complications, Arch. Int. Med. **61**:693 (May) 1938.

4. (*a*) Lloyd, R. I.: Arachnodactyly (Dystrophia Mesodermalis Congenita, Typus Marfanis; Marfan's Syndrome; Dolichostenomelia), Arch. Ophth. **13**:744 (May) 1935; (*b*) Second Group of Cases of Arachnodactyly, ibid. **17**:66 (Jan.) 1937. (*c*) Burch, F. E.: Association of Ectopia Lentis with Arachnodactyly, ibid. **15**:645 (April) 1936. (*d*) Pino, R. H.; Cooper, E. L., and Van Wien, S.: Ann. Int. Med. **10**:1130, 1937. (*e*) Norcross, J. R.: J. Bone & Joint Surg. **20**:757, 1938.

5. Méry, H., and Babonneix, L.: Bull. et mém. Soc. méd. d. hôp. de Paris **19**: 671, 1902.

6. Piper, R. K., and Irvine-Jones, E.: Arachnodactylia and Its Association with Congenital Heart Disease: Report of Case and Review of Literature, Am. J. Dis. Child. **31**:832 (June) 1926.

7. Dubois, M.: Ann. Soc. méd.-chir. de Liège **52**:281, 1913.

In the case to be reported all of the foregoing abnormalities were present and, in addition, there was a significant secondary anemia of long duration. Salle,[8] Börger[9] and Piper and Irvine-Jones[6] reported cases of arachnodactyly in which autopsies were performed. Futcher and Southworth[3] added a note on an unpublished autopsy performed by Rambar and Denenholz. The case to be reported appears to be the fifth case in which autopsy was performed.

## REPORT OF A CASE

The subject of this report was a German-born girl who died a few months before she was 16 years of age. Her parents and a sister had no bony deformity, no manifest disturbance of the endocrine glands and no evidence of syphilis. She was a full term infant weighing 7½ pounds (3,401 Gm.) at birth but was delicate. When she was about 6 months old, she had convulsions at hourly intervals for a period of several days. During the first year of her life it was noticed that her fingers and toes were unusually long. At this time she was in a hospital in Munich for four months for orthopedic treatment apparently directed toward correction of a severe deformity of the thoracic portion of the spine. She walked and talked when 1 year old. An operation was performed in Wurzburg when she was 3 years old for treatment of a congenital dislocation of the left hip.

Her vision was poor in early childhood. An unsuccessful ophthalmic operation was performed in a New York hospital when she was 7 years old. Dr. Goldstein (New York Eye and Ear Infirmary) removed a cataract from the right eye when she was 10 or 11 years old.

She was first admitted to the outpatient department of the New York Hospital in June 1934, when nearly 13 years old. At this time her weight was 32.7 Kg. and her height 153 cm. The length of the upper part of the arms was 29 cm., of the forearms 29 cm. and of the middle fingers 9 cm. The right leg from the knee down was 47 cm. in length, the left leg 46 cm. and each foot 24 cm. The fingers were long and thin (spider fingers), and the toes were sharply flexed toward the plantar surface (hammer toes). There was advanced kyphoscoliosis, with the convexity pointing posteriorly and to the left. She was pale and emaciated. The heart was slightly enlarged to the left, and a loud systolic murmur was heard over the entire precordium. There were coarse rales at the bases of the lungs. No deep muscular reflexes could be elicited. There was some hair on the pubes. She had not menstruated.

Examination of the blood showed a hemoglobin content of 5.1 to 5.8 Gm. per hundred cubic centimeters and a red cell count of 3,400,000 per cubic millimeter. These cells were pale; and macrocytes, microcytes and an occasional normoblast were present. There were 9,200 white blood cells, with 55 adult polymorphonuclears, 41 lymphocytes, 3 monocytes and 1 eosinophil per hundred leukocytes.

Roentgenographic examination showed advanced scoliosis, bowing of the humeri, early closure of the epiphyses of the olecranon processes and humeri, a partial fusion of the epiphyses of the distal ends of the tibia and fibula, to be expected in a girl 18 months older than the patient, and early closure of the sutures of the skull. The left acetabular cavity was irregular. The head of the left femur was displaced downward and the trochanter displaced upward with shortening

8. Salle, V.: Jahrb. f. Kinderh. **75**:540, 1912.

9. Börger, F.: Ztschr. f. Kinderh. **12**:161, 1914.

of the neck of the femur. The bones showed no definite abnormality of form or structure. The anterior clinoid process was sharp and the sella turcica not enlarged.

Examination of the eyes by Dr. Bernard Samuels showed that the right lens had been removed and that there was a congenital cataract of the left. Vision could not be improved above 20/50 for the right and 20/200 for the left eye with the use of glasses.

In January 1935, when the patient was 13½ years old, she was receiving treatment with iron ammonium citrate. Examination of the blood showed a hemoglobin

Fig. 1.—A photograph of the patient when 13½ years old, which shows the extreme kyphoscoliosis and relative elongation of the extremities.

content of 7.3 Gm. and a red cell count of 3,250,000. The cells were pale on smear, and there was poikilocytosis. Macrocytes and microcytes were present.

Dyspnea and pain in the chest developed, and the patient was admitted as an inpatient to the pediatric service of Dr. Samuel Z. Levine in June 1935, when 14 years old.

At that time the heart was enlarged 10 cm. to the left and 3 cm. to the right of the midline in the fifth interspace. The veins over the chest were prominent. The extremities showed the lesions already reported. The head was large, with a symmetric contour and a high prominent forehead. The photographs taken at

this time showed these deformities (figs. 1 and 2). The bony palate was long, narrow and highly arched. The patient was intelligent.

The temperature was not elevated above 38 C. (100.4 F.) except once when on the day after a transfusion it reached 39.4 C. (103 F.).

The hemoglobin content was now 7 Gm. (45 per cent[10]), and there were 2,750,000 red blood cells. Achromia was advanced. There were 7,000 white blood cells. Of 100 leukocytes, 52 were adult polymorphonuclears, 8 immature polymorphonuclears, 34 lymphocytes, 3 monocytes and 3 eosinophils. The Kline diagnostic and Wassermann reactions were negative. There was a positive reaction to the intracutaneous injection of 0.1 mg. of tuberculin. The basal metabolic rate was —5 per cent.

Fig. 2.—A photograph of the patient's hands, which shows the extreme elongation of the digits and metacarpals, "spider fingers."

The right pupillary opening was double, with an artefact in the upper part of the iris. The left lens was dislocated, and it could be seen in the lower part of the pupil.

The patient improved somewhat in a convalescent hospital. In July 1936 there was no dyspnea or orthopnea. The systolic blood pressure was 110 mm. of mercury and the diastolic 70 mm.

The patient's last admission to the hospital (to the medical service of Dr. Eugene F. DuBois) was on May 13, 1937, when 15¾ years of age. At this time the mucous membranes were exceedingly pale, and there was slight edema of the ankles. The temperature was between 38 C. and 39.4 C. The pulse rate was between 120 and 140, and the respiratory rate around 40. There was 18 per cent

10. In this hospital 14.5 Gm. of hemoglobin per hundred cubic centimeters of blood is taken as 100 per cent.

of the normal hemoglobin content of the blood, and the red cell count was 1,800,000 per cubic millimeter. There were 9,800 leukocytes. Of 100 cells, 26 were adult polymorphonuclears, 46 were immature polymorphonuclears, 13 were lymphocytes and 15 were large mononuclear cells. The blood smear showed advanced hypochromia and also polychromatophilia. Examination of the urine showed no abnormality except a faint trace of albumin. The blood urea nitrogen was 23 mg. per hundred cubic centimeters (slightly elevated), the serum protein 3.8 Gm. (low), the blood cholesterol 196 mg. (within normal limits), the serum calcium 9.9 mg. (normal), the serum phosphorus 4.7 mg. (normal) and the serum phosphatase (fasting) 3.2 mg. per hundred cubic centimeters.

The patient was given a blood transfusion and put in an oxygen tent, but she died on the day after admission.

*Postmortem Examination.*—There were scars of operative incisions in both corneas. The pupils appeared as they were described during life. The eyes were not enucleated at necropsy.

The head was broad, the distance between the malar bones being especially great. The lower jaw was not prominent.

The trunk was greatly deformed, with a kyphos that measured 15 cm. in the long axis of the body and 10 cm. transversely, presenting in the midline of the midthoracic region. Also, the middle part of the sternum protruded anteriorly. On account of the spinal curvature, the relative shortening of the trunk as compared with the limbs was exaggerated, but even without this deformity the disproportion would have been significant. The length of the body was 155 cm. (5 feet 1 inch). The weight was 35.5 Kg. (78 pounds). The arms were 79 cm. (2 feet 7 inches) long from the top of the shoulders to the tip of the fingers. The right lower extremity was 106 cm. (3 feet 6 inches) from the anterior superior spine of the ilium to the ball of the foot; the left was slightly shorter. The hands, and especially the fingers, were long and narrow. The latter were tightly flexed at necropsy (performed nine hours after death), although they were straight during life. The feet and toes also were abnormally long, and there was firm flexion of the achilles tendon at autopsy. The head of the left femur was incompletely divided into two parts by a shallow groove on its upper surface. The boss medial to this groove was the larger, and it articulated with an irregular cavity on the outer aspect of the pelvic girdle. The lateral boss prevented complete adduction and internal rotation of the femur. The angle between the neck and the shaft of the femur approached a right angle.

The breasts were small, and the pubic hair was scanty. The general appearance indicated a person much older than her actual age.

The thyroid was small. A cyst about 1 cm. across occupied the lower pole of the right lobe. Microscopically, the vesicles varied in size. They were lined by flat cuboidal epithelium. The stroma was dense and contained lymphocytes in moderate numbers. The parathyroids were not identified. Anterior to the pericardium there were several small fibrous masses containing thymic tissue, with the structure typically seen on microscopic examination.

The pericardium contained 86 cc. of clear yellow fluid with a specific gravity of 1.015. The heart weighed 520 Gm., and both ventricles were enlarged. The musculature was pale and flabby. The left ventricular wall was 12 mm. and the right 4 mm. thick. There were two perforations in the center of the posterior cusp of the mitral valve, separated by a narrow horizontal strip of tissue. The upper opening, shaped like an arrow with its point toward the ventricle, was 3 mm. long. One of the chordae tendineae was attached to the triangular tissue above this cleft. The lower opening measured 3 mm. in the horizontal direction and

1 mm. vertically. Because of the thin margins of the openings it was postulated that the fenestration was congenital. Above this area several nodular calcified masses projected into the lumen of the valve, and the entire auriculoventricular ring was calcified. On the line of closure of the posterior cusp of the mitral valve there were two friable pale red elevated masses, the larger 2 mm. across. The lesion was considered an acute inflammatory condition. The circumferences of the valvular rings were: mitral, 14 cm.; aortic, 9.5 cm.; tricuspid, 12 cm., and pulmonic, 8 cm. The coronary arteries showed no lesion.

The pleural cavities contained no fluid, and there were no adhesions. The lungs weighed 650 Gm. together and were dark red and boggy. The alveoli contained air and frothy fluid. Microscopically, the alveoli contained a few polymorphonuclear cells and a little granular fibrin.

The aorta was small, with only a few lipoid plaques in its intima. There was a small soft friable thrombus in the left femoral vein just below Poupart's ligament.

The peritoneum contained 70 cc. of clear yellowish fluid with a specific gravity of 1.015. The vaults of the diaphragm were high, namely, at the level of the third rib in the right and the fourth rib in the left midclavicular line. The anteroposterior dimension of the cavity was greatly encroached on by the spinal deformity, which was even more evident from within the body than when viewed externally. As the column was traced downward it formed three sharp convexities, the first pointing to the right, the second to the left and the third to the right. The parts of the column between these bends lay almost superimposed on one another.

The liver weighed 1,130 Gm. and was yellowish brown, with indistinct vascular markings. There was a small area of perihepatic fibrosis over the left lobe.

The pancreas appeared normal on both gross and microscopic examination.

The middle part of the stomach was so ptosed that its greater curvature extended below the umbilicus. The mucosal folds in the fundus were thickened, and the mucosa toward the pylorus was mamillated. Microscopically, there was an extensive infiltration of the gastric mucosa by lymphocytes and plasma cells. There were moderately large nests of lymphocytes adjacent to the muscularis mucosae. The loop of the duodenum also extended abnormally far inferiorly. The agminated and discrete lymph follicles of the terminal portion of the ileum were moderately enlarged, as were the mesenteric lymph nodes.

The spleen was small and weighed 80 Gm. The consistency was slightly increased. The capsule was almost smooth. The cut surface was dark red. A firm grayish white infarct, 2 mm. across, and two small cysts were present under the capsule. No polymorphonuclear leukocytes were present on microscopic examination.

The adrenals each weighed 4 Gm. Their dimensions, especially their thickness, were less than normal. Microscopically, the cortical structure was intact, and the cells contained lipoid vacuoles in moderate numbers.

Each kidney weighed 140 Gm. The right was normal in shape, while the left was located in the pelvis of the body with its hilum at the center of one of the flat surfaces.

The vagina and cervix were long, and the corpus uteri was small. The relative size of the organs was similar to that found before puberty. The ovaries showed no superficial scars. On section, they were dark red except for a few small cysts. Microscopically, these cysts were lined with cuboidal epithelium. Immature and mature follicles were present, but they were found in small numbers.

The marrow of the vertebrae, sternum and upper end of the femur was dark red. Microscopically, the bone marrow from these regions was moderately hyperplastic, but there was a moderate amount of fat. The cells included myelocytes—

some of them eosinophilic—moderate numbers of polymorphonuclear cells, primitive erythroblasts in moderate numbers and many normoblasts. The marrow from the head of the tibia was yellow and on microscopic examination consisted almost entirely of fat. The cortical bone was histologically normal.

The brain was examined by Dr. Lewis D. Stevenson. The vessels of the circle of Willis were delicate and thin walled. Both frontal lobes were short. The cortex of the frontal lobes was atrophic, and the arachnoid was somewhat thickened over them.

The pituitary was 17.5 mm. in the lateral, 11 mm. in the anteroposterior and 6 mm. in the vertical dimension. Four microscopic sections were made, and there was no adenoma. The cells were present in normal proportions, with no increase in either the basophils or the eosinophils. In the pars intermedia there were a number of colloid-containing cysts. There was a cyst that measured about 3 mm. across in the posterior lobe.

*Bacteriologic Examination.*—Culture of the heart's blood contained Bacillus coli communis.

## COMMENT

It is clear that the immediate cause of death in the case reported was infection manifested by an acute vegetative endocarditis and bronchopneumonia. These conditions appeared to be of short duration. The underlying severe anemia was undoubtedly of great importance in causing the death of the patient.

There were a number of lesions indicating disorder of the endocrine glands. These included the small size of the adrenals, the cysts of the pars intermedia and pars nervosa of the pituitary, the cyst of the thyroid, the deficiency of follicles in the ovary and hypoplasia of the uterus. Cysts of the pituitary have been reported in previous cases of arachnodactyly. Salle [8] described cysts in the anterior lobe of the pituitary and in the tissue between the anterior and the posterior lobe. Börger [9] found cysts in the pars anterior and the pars media of the pituitary. However, Ganther [11] expressed the belief that these cysts are of normal occurrence in the pituitary. The persistence of thymic tissue, the hyperplasia of Peyer's patches and solitary follicles of the ileum and the hyperplasia of the mesenteric nodes are not unusual. In view of the fact that the bony and other anomalies of development clearly originated during intrauterine life, it seems impossible to attribute any etiologic significance to these minor anomalies of the glands of internal secretion.

The anomalies of development may be discussed as they were found in the heart, the brain, the bony and muscular structures and the eyes. The fenestration of the mitral valve of the heart was clearly a developmental anomaly without functional significance. The heart was found to be enlarged at the first physical examination included in the available records, three years before death.

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11. Ganther, R.: Ztschr. f. Kinderh. **43**:724, 1927.

The subnormal length of the frontal lobes of the brain was clearly due to incomplete development. The intelligence of the patient was not impaired. The absence of mental stigmas is the rule in arachnodactyly.

The bones showed a disproportionate lengthening that commenced early in life and was advanced when the patient was first seen at this hospital, when she was about 13 years old. At this time the epiphyses of the olecranon, the distal end of the femur and the distal ends of the tibia and fibula were seen in roentgenographic examination to be prematurely fused. The sutures of the skull also showed early closure. It is of interest to recall that in chondrodystrophy (or achondroplasia), an anomaly of osteogenesis, there is a direct contrast to the lesions of arachnodactyly. In the former disorder the long bones are short and thick and abnormal islands of cartilage may persist at the epiphysial lines and in the substance of the bones until puberty.[12] On the other hand, the patient with arachnodactyly has long thin bones and early disappearance of the cartilage of the epiphyses.

The spinal deformity, as seen on roentgenographic examination and at autopsy, appeared to be largely due to lack of support by the soft parts. The structure of the vertebral bodies themselves was not unusual.

With relation to the lesions of the eyes associated with arachnodactyly, Burch [4c] stated: "The phenomenon of arachnodactyly is undoubtedly due to a mesoblastic growth anomaly; at least, only mesoblastic tissues, with the exception of the eyes, are involved. The suspensory ligament of the lens is probably of ectodermal origin." On the other hand, Pino, Cooper and Van Wien [4d] said that "congenital dislocation of the lens can be explained by an anomaly of the embryonic vascular system, a mesodermal derivative," and again that "it is conceivable that any dystrophy of the mesoderm in embryonic life could cause dystrophic changes in the *tunica vascularis lentis* (a mesodermal derivative) and so to the lens and the iris."

In arachnodactyly the repeated association of bony changes of the extremities and spinal column with displacement of the lenses of the eyes and congenital cataracts and the not infrequent concomitant congenital dislocation of the hip indicates that these lesions arise from a congenital defect in structure. The familial incidence of arachnodactyly in cases in the literature supports this contention, although no familial history was demonstrated in the case reported here.

The lesions in the case reported are perhaps explainable as correlated anomalies of development which, except for the cortical atrophy, arose in derivatives of the middle germ layer. The anemia may perhaps be explained on a similar developmental basis. It was very severe, and it persisted for at least two years and, presumably, for much longer. There

12. Opie, E. L., and Allison, N.: J. M. Research **36**:277, 1917.

was a definite erythropoietic hyperplasia of the vertebral, sternal and femoral bone marrow at autopsy. No reference has been found to any type of anemia associated with arachnodactyly in the literature. Burch [4c] stated that the blood count was usually normal in arachnodactyly. The blood count in the case described is entirely unlike the primary anemias and erythroblastosis of childhood described by Fanconi.[13] The characteristic lesion in the case reported in this paper is the relatively and absolutely greatly diminished hemoglobin content. Seven blood counts were made during the year the patient was between 13 and 14 years of age; the hemoglobin content ranged between 4.6 Gm. and 8.1 Gm. (32 to 56 per cent [10]) per hundred cubic centimeters of blood, while the number of red blood cells ranged between 2,750,000 and 3,900,000 per cubic millimeter. On the last admission, two years later, the hemoglobin content was 2.6 Gm. (18 per cent), and the red blood cells numbered 1,800,000. This last count was the only one that seems likely to have been influenced by the endocarditis.

## SUMMARY

A girl 16 years old had arachnodactyly with the usual features of Marfan's syndrome, namely, long thin bones, kyphoscoliosis, congenital cardiac anomalies and cloudiness and displacement of the lenses of the eyes. There were also present congenital dislocation of the hip, a misplaced kidney and atrophy of the frontal lobes of the brain. Cysts were present in the thyroid and pituitary glands, and the ovaries contained an abnormally small number of follicles, but no etiologic significance was attributed to these abnormalities of the endocrine glands. The patient had a severe anemia of secondary type, with greatly diminished hemoglobin. The bone marrow contained an increased number of normoblasts and primitive erythroblasts. Evidence is presented indicating that arachnodactyly with the anomalies associated with it in this case is an anomaly of development especially manifest in the middle germ layer.

13. Fanconi, G.: Monatschr. f. Kinderh. **68**:129, 1937.

# CONGENITAL ABSENCE OF THE ABDOMINAL MUSCLES AND GENITOURINARY MALFORMATION

## REPORT OF TWO CASES

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The congenital anomaly of absence of the abdominal muscles is rarely seen and is constantly associated, when seen, with a variety of genitourinary anomalies, which always include hypertrophied bladder and usually include dilated and hypertrophied ureters, cystic degeneration of the renal tissues and cryptorchidism. These urinary anomalies are often associated with urethral obstruction of some type, and some authorities, notably Housden, have expressed the belief that urethral obstruction is present for at least an early part of fetal life in all cases of absence of abdominal muscles and causes secondarily dilatation of the bladder, pressure reabsorption of the anlage of the abdominal musculature, dilatation of the ureters, pressure dilatation of the renal tubules with cystic degeneration and nondescent of the testicles. However, there are few cases of absence of abdominal muscles reported in which an organic obstruction of the urethra was demonstrated—in fact, I believe only 2, 1 by Housden [1] and 1 by Lichtenstein.[2] It is difficult to understand the cases of gross urethral obstruction, with the same pressure anomalies of the genitourinary tract but with an entirely intact group of abdominal muscles. The cases in this report represent these two types: first, absence of abdominal muscles with a normal urethra and second, normal abdominal muscles with an obstructed urethra.

### REPORT OF CASES

CASE 1.—E. N., born June 10, 1939, the first child of Italian parents, was delivered without complications. His birth weight was 2,865 Gm., and his appearance was unusual in that the full, large abdomen was covered with thin skin which showed the pattern of many intestinal loops and one central longitudinal fold containing the umbilicus. Peristaltic motion could be watched in the intestinal loops. The costal margin was tilted forward and twisted slightly, so that it was prominent on the left. The head showed much molding, overriding of the parietal

1. Housden, L. G.: Congenital Absence of the Abdominal Muscles, Arch. Dis. Childhood **9**:219 (May) 1934.

2. Lichtenstein, B. W.: Congenital Absence of Abdominal Musculature, Am. J. Dis. Child. **58**:339 (Aug.) 1939.

and frontal bones and a prominent left posterior boss. The ears showed slight deformity of the pinnae. The extremities displayed increased muscular tonus, and the infant tended to take a position of opisthotonos, because there was no counteraction to the erector spinae group of muscles. Bilateral talipes equinovarus and a pilonidal sinus were present. In the abdomen could be palpated through the thin, relaxed and redundant abdominal wall a normal-sized liver, left kidney, spleen, many loops of small and large intestine, which could be felt in peristalsis, a large right kidney reaching to the umbilicus and a thick-walled bladder, apparently cone shaped and attached to the umbilicus. Immediately after the child's delivery transillumination showed a distended bladder, reaching upward to the umbilicus and giving the appearance of being in a longitudinal fold in the skin. The testes were not descended, but the scrotum was normal. The infant's measurements were all normal and were occipitobregmatic: head circumference, 34 cm.; chest circumference, 29.5 cm.; abdominal circumference, 32.5 cm., and length, 51 cm. The cystic function was normal, a large amount of urine having been passed easily. Catheterization of the urethra showed no obstruction.

Fig. 1.—E. N., aged 2 days. *A* shows the relaxed abdominal wall with a shift of the abdominal contents toward the left. *B* shows the pattern of the bladder and intestines, spastic flexion of the extremities, a prominent costal margin, a prominent left parietal boss and club feet.

Feedings were taken well and digestion seemed normal, but crying was very weak. Cystograms taken June 19 showed a large and somewhat irregular bladder. The temperature rose to 102 F. on June 26 and the urine showed many clumps of white cells, indicating acute cystitis and pyelitis. The blood contained 12.6 Gm. of hemoglobin per hundred cubic centimeters, 3,900,000 erythrocytes and 25,500 leukocytes, with 83 per cent polymorphonuclear leukocytes, 1 per cent eosinophils, 8 per cent small lymphocytes, 4 per cent juvenile forms, 2 per cent myelocytes and 2 per cent premyelocytes. There was also some anisocytosis, and some red cells larger than normal were present. In spite of transfusion and supportive treatment, the infant died on June 28, aged 16 days.

The outstanding pathologic feature of this case, a detailed description of which follows, were an enlarged cystic right kidney, an enormous right ureter with obstructing valves, a large bladder with a thick wall, a urachus extending to the umbilicus and absence of abdominal muscles. The normal urethra easily admitted catheterization and probing from the inside.

*Autopsy Report.*—External Appearance: The body, 48 cm. in over-all length, weighed 3,840 Gm. The left parietal boss was prominent. The left side of the chest was more noticeable than the right, and the lower ribs on the left side

Fig. 2.—E. N. after removal of the gastrointestinal tract; the genitourinary organs are in situ.

protruded as bony eminences. There was a superficial abrasion 2 cm. in diameter at the level of the second rib just to the left of the sternum. The abdomen, 45 cm. in circumference, was free of striae or other markings. It was saccular, with a doughlike consistency, devoid of elasticity, and the abdominal organs could be outlined with ease. The umbilicus was slightly inverted, its external surface pale and hyalin-like and free of cornification. Two centimeters superior to the anus was a cleftlike opening 1 cm. in depth. The external genitalia were normal. Bilateral equinus varus was present to a moderate degree. The abdominal wall was grossly devoid of musculature and 4 to 5 mm. in thickness. The pannicular fat was pale and lobulated.

Abdominal Cavity: The peritoneal cavity contained approximately 300 cc. of a clear yellow fluid, and the peritoneal surfaces were smooth. The stomach was tremendously dilated. The edge of the liver was 4 to 5 cm. below the costal border.

Kidneys: The left kidney weighed 22 Gm. The capsule stripped with ease, revealing a thin, soft, reddish brown cortical surface. On section the cortical and medullary areas were ill defined, and the usual architecture could not be made out. The parenchyma was a pale uniform red. The pelvis and calices were dilated, their linings thin and shiny, and they contained a small amount of cloudy yellow

Fig. 3.—Genitourinary organs of E. N.

fluid. There was no exudate or gross inflammatory reaction. The ureter was slightly dilated to a diameter of 6 mm. at the renal end, gradually enlarging to a diameter of 1.2 cm. near the bladder. The walls were somewhat thickened. A probe could be passed from the distal opening superiorly but not from the renal end downward. When the ureter was opened the mucosa was seen to be thrown into valvelike prominences at irregular intervals. Proximal to the valve were small sacculations which contained a little yellow fluid. The ureteral orifice in the bladder was patent.

The right kidney weighed 160 Gm. and measured 9 by 5 by 3.5 cm. Its capsule stripped with ease, presenting a fairly smooth, soft, reddish cortical surface. On

section the stroma was quite thin and the medullary-cortical boundary obscure and pinkish red. The markings were indistinct. The calices and pelvis were markedly dilated, containing a yellow fluid; the lining was smooth. The ureteral orifice and pelvis were markedly dilated; the ureter, dilated throughout its course, reached a maximum diameter of 3.5 cm. Its wall was thin and the mucosa thrown into numerous valvelike folds. A probe could be passed from the ureteral orifice of the bladder superiorly but not from above downward.

Pelvic Organs: The bladder, prostate and 2 cm. of the posterior urethra were removed in toto. The cavity of the bladder was small and contained several cubic centimeters of urine. The mucosa was intact, thickened and covered with a thin, clear jellylike substance. The musculature of the wall was hypertrophied, 8 mm. in thickness and of a firm consistency.

The prostate was small and composed of soft white tissue. Section of the attached posterior portion of the urethra and prostate revealed no evidence of organic obstruction. A probe could be passed through the anterior portion of the urethra with ease.

The testicles were small ovoid bodies 1.5 by 0.5 cm., lying free in the lower part of the abdominal cavity near the posterior wall.

Microscopic Examination: No muscle fibers were demonstrated in sections from various portions of the abdominal wall.

*Anatomic Diagnosis.*—The diagnosis on the basis of the foregoing observations was: hypertrophy and rotation of the bladder; atresia, obstruction by valves and dilatation of the ureters; bilateral cystic degeneration of the kidneys; complete absence of the abdominal musculature; cryptorchidism; pilonidal sinus, and bilateral talipes equinovarus.

The following report is of a case of congenital urethral obstruction associated with thin but intact abdominal muscles and a variety of genitourinary anomalies.

Case 2.—N. G., the second of twins, was born on Sept. 9, 1939. The other twin was normal. The parents were American, 30 and 28 years of age, and pregnancy was normal; the second twin, born by breech extraction, was deformed and cyanotic and lived only a few hours. The infant's weight was 1,760 Gm.; its placenta weighed 350 Gm. and its umbilical cord was 81 cm. long. The infant looked small; the abdomen protruded and was enormously enlarged. The skin of the abdominal wall was so thin as immediately to recall the preceding infant, E. N., who was born three months earlier, and to suggest the same diagnosis. The infant was given oxygen and 5 per cent carbon dioxide but died in five hours.

*Autopsy Report.*—The body, 41 cm. in length, had a loose, thin skin over the abdomen through which the viscera were easily palpated. Neither testis was felt in the scrotum. The penis was enclosed in the scrotal sac, and on pressure approximately 4 mm. of the glans could be extruded through what appeared to be a small opening in the superior anterior portion of the scrotal sac.

Abdominal Cavity: The anterior abdominal wall had a maximum thickness of 5 mm., and in no part could muscle tissue be identified grossly. Filling the lower half of the abdomen and extending far laterally in the right lower quadrant was a markedly hypertrophied bladder. The remaining viscera were in normal position.

Kidneys: The right kidney weighed 5 Gm., measured 3 by 2 by 1.6 cm. and was in its normal anatomic position. Its capsular surface was studded by many small, smooth-lined, cystic structures, the largest 6 mm. in diameter, which on

section were filled with a clear yellow fluid. They had no demonstrable connection with the poorly defined calices and pelvis. What remained of the renal parenchyma was light brown and free of any architectural markings. The pelvis was poorly defined and partially replaced by a white fatty-like tissue. Connection with the superior end of the ureter could not be established. The right ureter was a tortuous thickened structure 4 cm. in length. The upper third was dilated to an approximate thickness of 7 mm. The wall was markedly hypertrophied. A fine probe could not be passed through the ureter, and on dissection uninterrupted passage could not be demonstrated.

The left kidney weighed 5 Gm. and measured 3 by 2.5 by 2 cm. It was similar in makeup to its mate, with the exception that its cystic structures were larger

Fig. 4.—Urinary organs of N. G., showing atresia of the ureter and the point of obstruction of the urethra.

but fewer in number. Uninterrupted continuity into the ureter could not be established. The left ureter, a thin fibrotic structure with a maximum diameter of 4 mm., showed no dilatation. A probe could not be passed through it.

Bladder: The bladder was a markedly dilated hypertrophied structure measuring 3.5 by 7 by 3 cm. The left ureter passed over its left lateral anterior aspect and entered the ureteral orifice located on the anterior wall of the bladder a bit to the right of the midline. The right ureter entered just opposite on the posterior wall, the bladder having rotated to the right approximately 90 degrees on a vertical axis. The wall had a maximum thickness of 1.2 cm., the increase, on section, appearing to be due to hypertrophy of the muscular elements. The mucosa was relatively smooth and pearl gray. At both ureteral orifices of the bladder was found a small smooth outpouching approximately 5 mm. in diameter. A probe could be introduced into the ureter on each side to a depth of approximately 4 mm.

The internal urethral outlet was located on the left side of the lower region of the bladder, and through it the probe could be introduced for approximately 2 cm. On section the urethral canal could be followed for approximately the same distance, at which point the channel ended blindly. The external urethral orifice was patent, and a probe could be introduced to a depth of 1 cm. Dissection revealed that this orifice ended blindly at that point.

Testes: The testes were small, ovoid, dark bodies 6 by 4 by 4 mm., lying in the posterior portion of both lower quadrants, their attachment consisting only of a thin cord.

Microscopic Examination: Specimens from the abdominal wall showed all muscular layers to be thin but present.

*Anatomic Diagnosis.*—The diagnosis on the basis of the foregoing observations was: congenital atresia of the urethra; hypertrophy and rotation of the bladder; bilateral atresia of the ureters; bilateral polycystic kidneys; thin abdominal musculature, and bilateral atelectasis of the lungs.

## COMMENT

Housden's [1] belief that absence of the abdominal muscles does not occur without enlargement of the bladder is, I believe, true in all 38 reported cases.[3] It is known, on the other hand, that great dilatation of the bladder may occur in fetal life without in any way affecting the actual development of the abdominal muscles, as shown by Schmidt,[3a] my own second case and others.[4] Housden's [1] explanation of this seeming incompatibility is that in the former cases of absence of muscles the obstruction always occurred at or near the ninth week of fetal life—extremely early—and, therefore, caused dilatation of the bladder and local pressure as soon as the allantoic sac was closed off from the bladder. Normally from this time on the urine would pass through the urethra into the amniotic fluid. But if obstruction and local pressure occur at this early phase of development, the muscle fibers of the three abdominal muscle sheets and the rectus muscles, which have already formed from ventral downgrowths of myotomes, may die from pressure anemia and be reabsorbed. The question, then, is what becomes of the urethral obstruction in late fetal life, because so far urethral obstruction has been found at autopsy in only 2 cases of absence of abdominal muscles. These two obstructions were a ridge from the anterior wall of the prostatic portion of the urethra and a valve of the posterior portion of the urethra.[3a] The scarcity of proved cases of urethral obstruction makes it difficult to accept this explanation, although the hypertrophy

3. (*a*) Schmidt, C. O.: Ein Fall von hochgradiger Dilatation der Harnblase, der Harnleiter und Nierenbecken infolge eines klappenartigen Verschlusses des Orificium urethrae internum, Ztschr. f. urol. Chir. **11**:158, 1923. (*b*) McClendon, S. J.: Agenesia of the Abdominal Muscles, Arch. Pediat. **51**:673 (Oct.) 1934. (*c*) Housden.[1]

4. Campbell, M. F.: Pediatric Urology, New York, The Macmillan Company, 1937, vol. 1, p. 340.

of the wall of the bladder shows that it has worked against an obstruction. To explain hypertrophy of the bladder with all abdominal muscles present, it is only necessary to visualize a urethral obstruction arising slightly later in fetal life, after the three sheets of abdominal muscle are well formed. Then obstruction of the urethra may still cause hypertrophy of the bladder, thinning of the abdominal muscles, ureteral dilatation, cystic degeneration of the kidneys and cryptorchidism and, in fact, may dwarf the entire structure of the infant, as witness the size of my patient—1,760 Gm.—without causing entire absence of the abdominal muscles.

The suggested possibility of degeneration, injury or malformation of the spinal cord has been amply studied and has seemed most unlikely. The microscopic sections of spinal cord in my cases were entirely normal.

The possibility of early, temporary urethral obstruction seems worthy of more interest, and in all such cases complete dissection of the urethra should be done, even though a catheter or probe does pass easily.

A case is reported of absence of the abdominal muscles with a normal urethra but dilatation and hypertrophy of the bladder, dilatation of ureters and cystic kidneys.

A case is reported of thin abdominal muscles with complete urethral obstruction, and in this case also hypertrophy and dilatation of the bladder, atresia of the ureters and polycystic kidneys were present.

The probability is recognized that urethral obstruction near the ninth week in fetal life causes destruction and reabsorption of the abdominal muscles and that later obstruction of the urethra causes thinning and weakening but not absence of these muscles.

The pathologic descriptions were prepared by Dr. L. J. Buis and Dr. F. J. Hartman, of the department of pathology, Henry Ford Hospital.

# Progress in Pediatrics

## SURGICAL AND MEDICAL TREATMENT OF EXOPHTHALMIC GOITER OF CHILDREN

### LATE RESULTS

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Since the year 1908, 171 children have been treated for exophthalmic goiter at the Mayo Clinic. A follow-up study was undertaken to determine the later status of these children. Of the entire group of 171, reports were secured from 163 patients. Of these 163, 138 had been treated surgically and 25 had been treated medically. The ratio of females to males for the entire group of 171 patients was 7.5 to 1 (table 1).

The ages of the 163 patients from whom late reports were received at the time of treatment are recorded in table 2. As is to be expected, the disease is to be found in the greater number of patients in the late years of childhood. It is also evident, however, that exophthalmic goiter was found among a fair number of very young children. If the time of onset of the disease is considered, it is evident from a table prepared a few years ago that the condition may be manifest during the first year of life.[1]

In table 3 the respective intervals between the time of treatment and the last report on the condition of the patients are recorded. The majority of the reports covered periods up to fifteen years after treatment, but a considerable number of the patients reported after intervals of sixteen to thirty-one years. Reports from patients treated medically do not go back more than sixteen years, for there was no recognized medical treatment of the disease before iodine was brought into use in 1922.

If the immediate results of surgical treatment in the group are considered, they were judged to be good in 111 of 138 patients, fair

From the Section on Pediatrics, the Mayo Clinic.

Read at the meeting of the American Pediatric Society, Skytop, Pa., May 2, 1940.

1. Kennedy, R. L. J.: The Thyroid Gland, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1937, vol. 1, chap. 38, pp. 1-43.

TABLE 1.—*Exophthalmic Goiter of Children; Distribution According to Sex and Treatment*

| Sex | Treatment | | Total |
|---|---|---|---|
| | Surgical | Medical | |
| Females | 130 | 21 | 151 |
| Males | 16 | 4 | 20 |
| Total | 146 | 25 | 171 |

TABLE 2.—*Traced Cases of Exophthalmic Goiter of Children*

| Age, Years * | Treatment | | Number of Cases |
|---|---|---|---|
| | Surgical | Medical | |
| 3 | 1 | .. | 1 |
| 4 | 3 | .. | 3 |
| 5 | 1 | 2 | 3 |
| 6 | 4 | 1 | 5 |
| 7 | 4 | 1 | 5 |
| 8 | 6 | 1 | 7 |
| 9 | 5 | 1 | 6 |
| 10 | 7 | 3 | 10 |
| 11 | 14 | 5 | 19 |
| 12 | 17 | 2 | 19 |
| 13 | 35 | 3 | 38 |
| 14 | 41 | 6 | 47 |
| Total | 138 | 25 | 163 |

* At time of treatment.

TABLE 3.—*Exophthalmic Goiter of Children; Interval Between Time of Treatment and Last Report*

| Interval | Treatment | | Total |
|---|---|---|---|
| | Surgical | Medical | |
| Less than 1 year | 13 | 7 | 20 |
| 1 year | 4 | .. | 4 |
| 2 years | 2 | 1 | 3 |
| 3 years | 4 | 1 | 5 |
| 4 years | 3 | 1 | 4 |
| 5 years | 4 | 2 | 6 |
| 6 years | 2 | .. | 2 |
| 7 years | 5 | 2 | 7 |
| 8 years | 6 | .. | 6 |
| 9 years | 7 | 2 | 9 |
| 10 years | 8 | 1 | 9 |
| 11 years | 14 | 1 | 15 |
| 12 years | 9 | 1 | 10 |
| 13 years | 11 | 1 | 12 |
| 14 years | 3 | 1 | 4 |
| 15 years | 8 | 3 | 11 |
| 16 years | 4 | 1 | 5 |
| 17 years | 1 | .. | 1 |
| 18 years | 2 | .. | 2 |
| 19 years | 5 | .. | 5 |
| 20 years | 1 | .. | 1 |
| 21 years | 5 | .. | 5 |
| 22 years | 2 | .. | 2 |
| 23 years | 1 | .. | 1 |
| 24 years | 1 | .. | 1 |
| 25 years | 4 | .. | 4 |
| 26 years | 1 | .. | 1 |
| 27 years | 4 | .. | 4 |
| 28 years | 2 | .. | 2 |
| 30 years | 1 | .. | 1 |
| 31 years | 1 | .. | 1 |
| Total | 138 | 25 | 163 |

in 18 and poor in 1 (table 4). There were 8 operative deaths in the entire group of 146 patients. When the results are arranged according to the year of operation, certain facts stand out clearly. Before iodine came into use in the preoperative preparation and the postoperative care of these patients—that is, before 1922—the results were considered good in 32.4 per cent of patients, but after iodine came into use the results were considered good in 67.5 per cent. The beneficial effects of iodine medication are further demonstrated by the fact that of the

TABLE 4.—*Exophthalmic Goiter of Children; Immediate Results According to Years of Operation (1908 to 1939)*

| Year of Operation | Immediate Results | | | Hospital Deaths | Total |
|---|---|---|---|---|---|
| | Good | Fair | Poor | | |
| 1908 | 2 | .. | .. | .. | 2 |
| 1909 | 4 | .. | .. | .. | 4 |
| 1911 | 1 | 1 | 1 | .. | 3 |
| 1912 | 4 | .. | .. | .. | 4 |
| 1913 | 2 | 2 | .. | .. | 4 |
| 1914 | 3 | 1 | .. | .. | 4 |
| 1915 | 3 | .. | .. | 1 | 4 |
| 1916 | 0 | 2 | .. | 1 | 3 |
| 1917 | 2 | 2 | .. | .. | 4 |
| 1918 | 6 | 1 | .. | .. | 7 |
| 1919 | 3 | .. | .. | 1 | 4 |
| 1920 | 4 | .. | .. | 1 | 5 |
| 1921 | 2 | .. | .. | 1 | 3 |
| 1922 | 1 | 1 | .. | .. | 2 |
| 1923 | 6 | 2 | .. | .. | 8 |
| 1924 | 4 | 1 | .. | .. | 5 |
| 1925 | 4 | 2 | .. | 1 | 7 |
| 1926 | 12 | .. | .. | .. | 12 |
| 1927 | 9 | .. | .. | .. | 9 |
| 1928 | 11 | 1 | .. | .. | 12 |
| 1929 | 7 | .. | .. | .. | 7 |
| 1930 | 6 | 1 | .. | .. | 7 |
| 1931 | 1 | .. | .. | 1 | 2 |
| 1932 | 4 | 1 | .. | .. | 5 |
| 1933 | 1 | .. | .. | 1 | 2 |
| 1935 | 1 | .. | .. | .. | 1 |
| 1936 | 3 | .. | .. | .. | 3 |
| 1937 | 2 | .. | .. | .. | 2 |
| 1938 | 2 | .. | .. | .. | 2 |
| 1939 | 1 | .. | .. | .. | 1 |
| Total | 111 | 18 | 1 | 8 | 138 |

55 patients operated on previous to 1922, 5 died in the hospital, whereas after 1922 there were only 3 deaths following operations on 91 patients. Thus, the surgical mortality rate before the use of iodine was 9 per cent, whereas after iodine came into use the mortality rate was only 3.3 per cent, in spite of the fact that before 1922 there were 19 patients treated only by ligation of one or both superior thyroid arteries, whereas after 1922 all patients were subjected to thyroidectomy.

The late results of treatment were studied by arranging the number considered as good, fair and poor according to the years in which the original operations were carried out (table 5). Results were considered to be good among patients who were free from symptoms of exophthalmic goiter and who were able to pursue their usual activities.

Results were considered fair among those patients for whom the disease had not been entirely controlled or among those for whom there continued to recur symptoms, such as nervousness, palpitation or exophthalmos, which might be ascribed to incomplete control of the disease. Results were termed poor among patients for whom the condition was not controlled. Based on these criteria, the late results were good among 106 patients, fair for 23 and poor for 1.

TABLE 5.—*Exophthalmic Goiter of Children; Late Results According to Year of Operation (1908 to 1939)*

| Year of Operation | Late Results | | | | Later Death | | | Subsequent Operation | Totals |
|---|---|---|---|---|---|---|---|---|---|
| | Good | Fair | Poor | Totals | Later Thyroid Death | from Other Cause | Recurrence | | |
| 1908 | 2 | .. | .. | 2 | 1 | .. | .. | .. | 1 |
| 1909 | 4 | .. | .. | 4 | .. | 1 | .. | .. | 1 |
| 1911 | 1 | 1 | 1 | 3 | 1 | 1 | 2 | 2 | 6 |
| 1912 | 4 | .. | .. | 4 | .. | .. | .. | .. | .. |
| 1913 | 2 | 2 | .. | 4 | .. | 1 | .. | 2 | 3 |
| 1914 | 3 | 1 | .. | 4 | .. | .. | .. | 1 | 1 |
| 1915 | 3 | .. | .. | 3 | .. | 1 | .. | .. | 1 |
| 1916 | .. | 2 | .. | 2 | 1 | 1 | .. | 1 | 3 |
| 1917 | 1 | 3 | .. | 4 | .. | 1 | 1 | 2 | 4 |
| 1918 | 6 | 1 | .. | 7 | .. | .. | 2 | 2 | 4 |
| 1919 | 3 | .. | .. | 3 | .. | .. | .. | .. | .. |
| 1920 | 3 | 1 | .. | 4 | .. | .. | 1 | 1 | 2 |
| 1921 | 1 | 1 | .. | 2 | .. | .. | .. | .. | .. |
| 1922 | .. | 2 | .. | 2 | .. | .. | 1 | 1 | 2 |
| 1923 | 6 | 2 | .. | 8 | .. | .. | 2 | 2 | 4 |
| 1924 | 4 | 1 | .. | 5 | .. | .. | 1 | 1 | 2 |
| 1925 | 4 | 2 | .. | 6 | 1 | 1 | .. | .. | 2 |
| 1926 | 12 | .. | .. | 12 | .. | 1 | 1 | .. | 2 |
| 1927 | 9 | .. | .. | 9 | .. | .. | .. | .. | .. |
| 1928 | 10 | 2 | .. | 12 | .. | .. | .. | .. | .. |
| 1929 | 7 | .. | .. | 7 | .. | .. | .. | .. | .. |
| 1930 | 6 | 1 | .. | 7 | .. | .. | 1 | 2 | 3 |
| 1931 | 1 | .. | .. | 1 | .. | .. | .. | .. | .. |
| 1932 | 4 | 1 | .. | 5 | .. | .. | .. | .. | .. |
| 1933 | 1 | .. | .. | 1 | .. | .. | .. | .. | .. |
| 1935 | 1 | .. | .. | 1 | .. | .. | .. | .. | .. |
| 1936 | 3 | .. | .. | 3 | .. | .. | .. | .. | .. |
| 1937 | 2 | .. | .. | 2 | .. | .. | .. | .. | .. |
| 1938 | 2 | .. | .. | 2 | .. | .. | .. | .. | .. |
| 1939 | 1 | .. | .. | 1 | .. | .. | .. | .. | .. |
| Totals | 106 | 23 | 1 | 130* | 4 | 8 | 12 | 17 | 41 |

* Eight hospital deaths bring total to 138.

During the course of years, 4 of the 130 patients heard from died of causes which could be ascribed directly to disease of the thyroid gland, whereas 8 died of unrelated causes.

Twelve patients experienced recurrences. The recurring condition in some cases was mild and was easily controlled by the administration of iodine. In other cases subsequent operation became necessary. In 1 case operation was followed after some years by a recurrence. Resection of the gland was therefore repeated, after which myxedema developed. After another interval of years, a second recurrence of exophthalmic goiter took place and necessitated a third resection. Of the 130 patients heard from, subsequent operations were done on 17.

When the year of the original operation is considered, the number of later deaths from disease of the thyroid gland, the frequency of recurrences and the necessity for subsequent operation take on special significance. All of these incidents were much more frequent among the patients operated on before the time that iodine was employed as an essential part of the treatment than afterward. Three of the 4 later deaths that were due to disease of the thyroid gland, 6 of the 12 recurrences and 11 of the 17 subsequent operations took place during the

TABLE 6.—*Exophthalmic Goiter of Children; Incidence of Low Basal Metabolic Rate Among Patients Treated Surgically, According to Year of Operation (1908 to 1939)*

| Year of Operation | Patients | Patients with Low Basal Metabolic Rate |
|---|---|---|
| 1908 | 2 | .. |
| 1909 | 4 | .. |
| 1911 | 3 | 1 |
| 1912 | 4 | .. |
| 1913 | 4 | .. |
| 1914 | 4 | .. |
| 1915 | 4 | .. |
| 1916 | 3 | .. |
| 1917 | 4 | .. |
| 1918 | 7 | 1 |
| 1919 | 4 | .. |
| 1920 | 5 | .. |
| 1921 | 3 | .. |
| 1922 | 2 | .. |
| 1923 | 8 | 3 |
| 1924 | 5 | 1 |
| 1925 | 7 | .. |
| 1926 | 12 | .. |
| 1927 | 9 | 2 |
| 1928 | 12 | 4 |
| 1929 | 7 | 2 |
| 1930 | 7 | 2 |
| 1931 | 2 | .. |
| 1932 | 5 | .. |
| 1933 | 2 | .. |
| 1935 | 1 | .. |
| 1936 | 3 | 2 |
| 1937 | 2 | 1 |
| 1938 | 2 | .. |
| 1939 | 1 | .. |
| Total | 138 | 19 |

earlier years. Furthermore, it is evident from table 5 that recurrences and the necessity for subsequent operations diminished rapidly as intensive iodine therapy became better developed.

Low basal metabolic rates or frank myxedema followed operation in 19 cases (table 6). Before 1922 these incidents were of relatively infrequent occurrence, there having been only 2 reports. This is easily explained by the fact that surgical procedures during the earlier years were much less extensive than they have been in later years. This in turn is directly attributable to the fact that preoperative iodine medication has permitted the surgeon to carry out resection of a much larger part of the gland than formerly, thereby controlling the disease in a greater percentage of cases. In some instances, the low metabolic rates

as well as the myxedema which followed operation, both of which were easily controlled by medication with desiccated thyroid, eventually disappeared.

Of the patients on whom surgical intervention was carried out, 12 had complications which were unrelated to diseases of the thyroid gland and were present at the time of operation or developed subsequently. In 1 case a cyst of the brain was thought to be a factor which contributed to the postoperative death. Addison's disease and diabetes mellitus each accounted for the later death of 1 patient. In 1 case

TABLE 7.—*Results of Medical Treatment of Exophthalmic Goiter of Children*

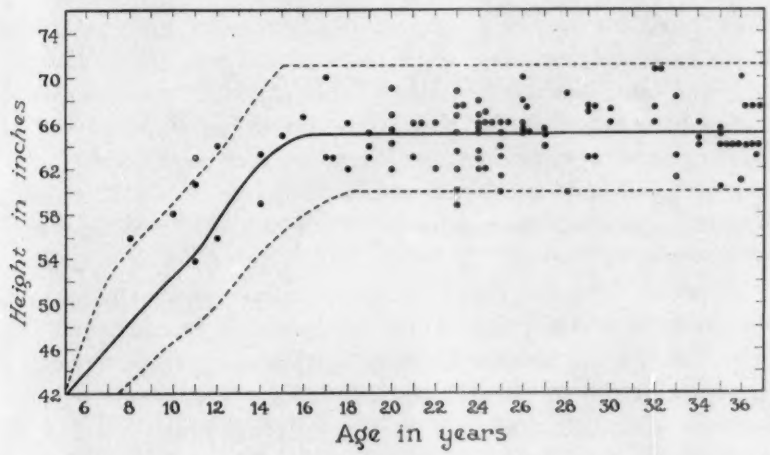
| Case | Sex | Age, Years | Basal Metabolic Rate | Compound Solution of Iodine U. S. P. | Interval Between Treatment and Last Report | Operation Elsewhere | Final Result | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Good | Fair | Poor | Dead |
| 1 | F | 6 | +21 | + | ? | + | .. | .. | .. | + |
| 2 | F | 14 | .... | + | 3 days | .. | .. | .. | .. | +* |
| 3 | F | 12 | +63 | .. | ..... | .. | .. | .. | .. | +† |
| 4 | F | 14 | .... | .. | 8 days | .. | .. | .. | .. | + |
| 5 | F | 14 | .... | .. | 6 mo. | .. | .. | .. | .. | +‡ |
| 6 | F | 11 | + 4 | + | 6 mo. | .. | .. | .. | + | .. |
| 7 | M | 13 | .... | .. | 3 mo. | + | + | .. | .. | .. |
| 8 | F | 11 | +11 | + | 2 yr. | .. | +? | .. | .. | .. |
| 9 | F | 5 | +43 | + | 3 yr. | + | + | .. | .. | .. |
| 10 | F | 7 | +22 | + | 3 yr. | + | + | .. | .. | .. |
| 11 | F | 11 | +24 | + | 4 yr. | .. | + | .. | .. | .. |
| 12 | F | 13 | +59 | + | 5 yr. | + | .. | .. | .. | .. |
| 13 | F | 10 | +28 | + | 7 yr. | .. | .. | + | .. | .. |
| 14 | M | 10 | +32 | .. | 7 yr. | .. | +‡ | .. | .. | .. |
| 15 | M | 14 | — 9 | + | 9 yr. | .. | .. | + | .. | .. |
| 16 | F | 14 | + 3 | + | 9 yr. | .. | + | .. | .. | .. |
| 17 | F | 10 | — 8 | + | 10 yr. | .. | + | .. | .. | .. |
| 18 | F | 11 | +22 | + | 11 yr. | .. | +§ | .. | .. | .. |
| 19 | M | 9 | +15 | + | 12 yr. | .. | + | .. | .. | .. |
| 20 | F | 12 | +36 | + | 13 yr. | .. | +‡ | .. | .. | .. |
| 21 | F | 8 | — 7 | + | 14 yr. | .. | + | .. | .. | .. |
| 22 | F | 5 | +33 | + | 15 yr. | .. | + | .. | .. | .. |
| 23 | F | 11 | —12 | + | 15 yr. | + | + | .. | .. | .. |
| 24 | F | 14 | +60 | + | 15 yr. | + | + | .. | .. | .. |
| 25 | F | 13 | +18 | + | 16 yr. | .. | .. | + | .. | .. |

* Bronchopneumonia.
† Mental deficiency.
‡ Operation refused.
§ Operation refused; later, adrenal cortical or Cushing's syndrome.

hirsutism and obesity made their appearance after some years, but other signs of specific endocrine dysfunction were not present. One case each of mitral stenosis, pulmonary tuberculosis, narcolepsy and psychosis was encountered. Two instances of mental retardation and 2 of hypertension occurred.

Twenty-five children came to the Mayo Clinic because of exophthalmic goiter. Operation was not performed (table 7), and the children were treated medically. Twenty-one of these patients were females, and 4 were males. The ages ranged from 5 to 14 years. Seven of the patients were operated on elsewhere after leaving the clinic; 1 of these died after the operation. Thus, only 18 eventually were treated by medical means alone, and of these 4 died. One died of pneumonia shortly after admission; 1, who was retarded in mental development, died later

from an undetermined cause; 1 was in a state of crisis on arrival and died after eight days, and another, for whom operation was refused, died after six months. Of the 15 for whom the ultimate outcome was judged to be good, 6 had operations elsewhere. In 1 case, the late status was questionable; in another, symptoms suggestive of either an adrenal cortical syndrome or Cushing's syndrome had made their appearance. It will be noted that the basal metabolic rates of 4 patients on admission to the hospital were on the minus side; these patients were thought to have relatively mild conditions. The outcome of medical treatment was fair in 1 of these 4 and good in 2; 1 of the patients was operated on elsewhere, with good results. Thus, in respect to medical management, it has been found that operation has become necessary in a number of




Distribution curve of height for 102 females treated surgically for exophthalmic goiter; average height of patients aged 21 and over, 5 feet and 5 inches (165 cm.).

cases but that in mild cases restriction of activity plus the administration of compound solution of iodine U. S. P. will carry some children through to an apparently normal adult status.

An attempt was made to determine whether patients who had suffered from exophthalmic goiter during childhood grew more rapidly in height than did children not so afflicted and whether they ultimately attained a greater height than the average adult. A curve was constructed to show the mean height, the minimal height and the maximal height of normal females from the figures of the Baldwin-Wood table (see chart). Figures representing the heights of 102 female patients who had received treatment for exophthalmic goiter during childhood were plotted along this curve. Inspection of the chart reveals the fact that among patients less than 18 years of age exophthalmic goiter apparently produced a stimulus to the rate of growth. However, the average height

of patients aged 21 and more was found to be the same as the average height of normal females, as judged by the extension of the mean height at 18 years of age calculated from the Baldwin-Wood table.


## SUMMARY

A follow-up study was made of 171 patients who had been seen at the Mayo Clinic during their childhood because of exophthalmic goiter. Reports were received from 163. Of those, 138 had been treated surgically and 20 had been treated medically. The ratio of females to males was 7.5 to 1. The ages ranged from 3 to 14 years. Reports were received from patients who had been operated on as long as thirty-one years previously and from patients who had been treated medically as far back as sixteen years previously.

The immediate results of surgical treatment were good or fair in most cases, but the permanent results of treatment were much improved after iodine came into use in 1922. Of 138 patients treated surgically, 106 experienced late results that were entirely satisfactory. In 23 instances results were fair, and in 1 instance they were poor. Recurrences were both mild and severe and were experienced by 12 patients. Subsequent operations were done on 17 patients. Most of these were patients originally operated on before the advent of iodine medication. Low metabolic rates and postoperative myxedema were more frequent in the group in which treatment was by the use of extensive resection than in that in which treatment was by ligation of vessels or by ligation and partial resection. In 12 cases pathologic conditions of major importance other than disease of the thyroid gland were present at the time of operation or developed subsequently.

Twenty-five patients were treated medically. Seven of them were operated on at some time subsequent to medical treatment. Of the patients who died, 3 were in a critical condition at the time of arrival at the hospital. In a few cases of mild involvement, the disease appears to have been controlled by medical treatment. Children with exophthalmic goiter apparently grow more rapidly than so-called normal children, but their heights ultimately are not greater than or less than the average height.

# News and Comment

## GENERAL NEWS

**The American Board of Pediatrics.**—An examination will be held in New York on March 30 and 31, 1941, following the meeting of the American Academy of Pediatrics, Region I, and another, in Chicago, on May 18, 1941, following the meeting of the American Academy of Pediatrics, Region III.

## UNIVERSITY NEWS

**University of California.**—Dr. Langley Porter has been made dean emeritus of the University of California Medical School.

# Abstracts from Current Literature

## Metabolism; Infant Feeding; Milk and Other Foods

THE EXCRETION OF FREE AND ACETYLSULFANILAMIDE IN HUMAN BREAST MILK. L. R. HAC, F. L. ADAIR and H. C. HESSELTINE, Am. J. Obst. & Gynec. **38**: 57 (July) 1939.

During the first nine days of the postpartum period, 25 normal lactating women were given from 2 to 5 Gm. of sulfanilamide. The drug was given in six doses daily for a period of three days. The levels of free and acetylated sulfanilamide were determined in the milk, blood and urine. The level of the drug in the milk was higher than that in the blood. Forty-eight hours after the administration of sulfanilamide had been discontinued, the drug was still being excreted in the milk in measurable but negligible amounts. The percentage of the sulfanilamide excreted in the conjugated acetyl form was low the first day the drug was given, increased slightly the second and the third day and rose sharply the fourth and the fifth day, when the administration of the drug had been discontinued. The percentage varied from 35.1 to 83.9. The same general course was observed in the blood and urine. After a fairly constant blood level had been established, the drug seemed to be excreted in the milk at a definite concentration per cubic centimeter rather than per total volume. The total amount of sulfanilamide excreted in the milk over a period of five days was never greater than 0.23 Gm., 1.6 per cent of the total dose ingested. The amount of the drug excreted in the milk was so small that there probably would be little danger to the nursing infant unless it was unusually susceptible to sulfanilamide.

ARENA, Durham, N. C.

OXALIC ACID IN FOODS AND ITS BEHAVIOR AND FATE IN THE DIET. E. F. KOHMAN, J. Nutrition **18**:233 (Sept.) 1939.

Kohman found that when rats between the ages of 21 and 90 days were fed a diet relatively low in calcium, which permitted good though not maximum growth and bone formation, even if spinach was added to the extent of about 8 per cent to supply 60 per cent of the calcium, a high percentage of deaths occurred. Reproduction was impossible. The bones were extremely low in calcium; tooth structure was disorganized and dentine poorly calcified. Oxalates have been shown to occur to the extent of about 10 per cent (on a dry basis, expressed as anhydrous oxalic acid) in spinach, New Zealand spinach, Swiss chard, beet tops, lamb's quarter, poke, purslane and rhubarb. Nearly all vegetables and fruits have shown traces. Kohman proved that not only does spinach not supply available calcium but it definitely renders unavailable a considerable part of that in other foods. The oxalate appeared mostly in the feces; however, a considerable amount was found in the urine.

FREDEEN, Kansas City, Mo.

EFFECT OF SEVERAL CALCIUM SALTS ON THE UTILIZATION OF LACTOSE. H. S. MITCHELL, G. M. COOK and K. L. O'BRIEN, J. Nutrition **18**:319 (Oct.) 1939.

Rats were fed an adequate ration containing lactose in a concentration of 60 per cent plus calcium to a concentration of 1.0 or 0.5 per cent, added in the form of six common calcium salts, namely, tricalcium phosphate, carbonate, citrate, levulinate, lactate and gluconate. After receiving the first four salts, the rats showed as good growth, less diarrhea in general, the same degree of galactemia and a similar incidence of cataract, as on the plain 60 per cent lactose ration. Calcium lactate was somewhat toxic at the higher level. Calcium gluconate was definitely toxic at both levels. Sodium gluconate exerted a deleterious effect

more severe than did calcium gluconate; it was assumed, therefore, that the gluconate radical may interfere with lactose activity in the intestinal tract, an interference, the authors postulate, possibly explainable by the "competitive inhibition" in enzyme action, due to the similarity of the lactose and the gluconate radical.

FREDEEN, Kansas City, Mo.

EFFECT OF HEAT AND SOLVENTS ON THE NUTRITIVE VALUE OF SOYBEAN PROTEIN. L. M. JOHNSON, H. T. PARSONS and H. STEENBOCK, J. Nutrition **18**:423 (Oct.) 1939.

By determining sulfur and nitrogen balances in rats, the authors confirmed previous observations that heat improves the nutritive value of soybean protein and thereby makes it available for tissue-building purposes. Certain solvents, such as hexane and methanol, did not have a similar effect.

FREDEEN, Kansas City, Mo.

INFANT OVERFEEDING. C. H. SMITH, M. Clin. North America **23**:569 (May) 1939.

There is a widespread tendency to overfeed the bottle-fed baby and to add foods other than the bottle formula too early and in inordinate amounts. Such overfeeding often results in vomiting, restlessness and failure to gain, which in turn are interpreted as due to malnutrition. It has never been shown that the normal infant requires more than about 45 calories per pound (100 per kilogram) of body weight. The infant's protein need is met by that contained in 1½ to 1¾ ounces of milk per pound of body weight. The addition of about 1/12 ounce per pound of added sugar will therefore supply the needed calories. The fluid requirements in the early months are 3 ounces per pound, and in the later months only 2 ounces per pound are required. Years of experience have proved that infants fed on this basis will thrive and make normal gains.

Fear of the early loss of weight in the newborn excites many physicians and leads to the forcing of various solutions and the giving of strong formulas. It should be borne in mind that the newborn infant normally receives very little food from the mother during the first two weeks of life and that when artificial feeding is necessary the formula should be correspondingly weak. Neglect of this fact is likely to upset the delicate digestion of these infants, and there is the further possibility of sensitizing them to cow's milk when the digestive tract is more permeable than it is later.

The conservative attitude of the author may strike some as being rather out of date, but the observations of such an experienced practitioner should be made "required reading" for the more enthusiastic members of the pediatric profession.

EUGENE H. SMITH, Ogden, Utah.

NUTRITIVE VALUE OF POWDERED WHOLE MILK. R. C. HUTCHINSON, M. J. Australia **2**:392 (Sept. 9) 1939.

Hutchinson reports on a detailed study of a chemical and biologic comparison between a popular Australian whole milk powder and fresh milk. Nothing new was uncovered.

GONCE, Madison, Wis.

BIOLOGIC STUDIES OF SUPERSONIC WAVES: THE EFFECT OF SUPERSONIC WAVES ON THE SURFACE TENSION AND HYDROGEN ION CONCENTRATION OF MILK. S. OGATA, Acta pædiat. japon. **45**:1069 (Aug.) 1939.

The surface tension and hydrogen ion concentration of human milk show a marked drop on the application of supersonic waves for from one-half to three minutes, whereas no changes are noted in cow's milk, goat's milk or powdered milk. These changes are due to activation of the lipase in the whey, which splits the milk fat, liberating fatty acids.

KATO, Chicago.

AN INQUIRY INTO BREAST FEEDING IN STOCKHOLM. S. RUDBERG, Acta pædiat. **24**:92, 1939.

The answers to a questionnaire submitted to 2,013 mothers revealed no evidence of a decline in the popularity of breast feeding; on the contrary, during the last five years the practice has become somewhat more common. Subsequent infants are apt to be fed at the breast longer than the first. Infants under the supervision of clinics enjoyed the benefits of the breast longer than those whose feeding was not supervised.

McCUNE, New York.

ACTIVITIES OF THE HELSINGFORS BREAST MILK STATION DURING THE EIGHTEEN MONTHS OF ITS EXISTENCE. T. SALMI, Acta pædiat. **24**:111, 1939.

Salmi reports that milk is collected from lactating women throughout the city of Helsingfors, Finland, that suitable safeguards are taken against adulteration with cow's milk or dilution with water and that sour milk is discarded. The milk is sterilized by heating for two minutes to a temperature between 70 and 80 C. In eighteen months 103 women yielded 7,965 liters of breast milk. The milk is distributed at various prices to public institutions and to private homes and finds a ready market. In all respects the operations of the collecting station have been highly successful.

McCUNE, New York.

## Vitamins; Avitaminoses

THE LARYNX IN INFANTILE BERIBERI. V. C. ALCANTARI and B. DECAMPO, Arch. Otolaryng. **30**:389 (Sept.) 1939.

Impairment of the mobility of the vocal cords should be added to the already recognized criteria for the diagnosis of infantile beriberi. The aphonic form of this disease, so called from the most frequent and most lasting symptom, is encountered in 80 to 90 per cent of all cases of infantile beriberi. The authors deplore the fact that, despite the significance of this symptom, the condition of the larynx in infantile beriberi has been studied but little in this country and abroad. It is suggested that in cases in which beriberi and acute infection of the respiratory tract coexist the motility of the cords is of help in determining whether both are present and what degree of deficiency of vitamin B exists in the child.

GREENWOOD, Chicago.

STUDIES IN THE USE OF CRYSTALLINE VITAMIN C (ASCORBIC ACID) IN THE PROPHYLAXIS AND TREATMENT OF INFANTILE SCURVY AND SOME OTHER DISORDERS OF INFANCY AND CHILDHOOD. A. S. KENNEY and M. RAPOPORT, J. Pediat. **14**:161 (Feb.) 1939.

Nineteen infants were given crystalline vitamin C in the dose of 1.83 mg. per kilogram of body weight daily for a period of five months, as a prophylactic against scurvy. No clinical or roentgenologic evidence of scurvy was apparent during the period of observation. Crystalline vitamin C was used in the treatment of 21 patients with infantile scurvy. The amount of ascorbic acid necessary to effect clinical healing varied from 100 to 500 mg., with an average of 310 mg. Thirteen infants with scurvy were treated with orange juice. It was assumed that a single ounce (28 Gm.) of orange juice contained 20 mg. of vitamin C. The amount necessary to effect the same degree of clinical improvement as was obtained with crystalline vitamin C varied from 80 to 1,080 mg., with an average of 510 mg. The effect of ascorbic acid on the anemia of scurvy was studied in 5 infants free from infection. In 3 of the 5 infants there was a significant increase in the red cell count, in the hemoglobin content or in both. Following the administration of vitamin C, no constant effect was observed on capillary resistance in the scorbutic infants as determined by a capillary fragility test. Crystalline vitamin C adminis-

tered to an infant operated on for pyloric stenosis seemed to stimulate healing of the wound; no evidence of healing was noted prior to the administration of this vitamin. Intravenously administered vitamin C seemed to have no effect on hematuria in a case of subacute hemorrhagic nephritis. RAUH, Cincinnati.

VITAMIN A REQUIREMENTS OF INFANTS. H. M. M. MACKAY, Arch. Dis. Childhood **14**:245 (Sept.) 1939.

The progress of a group of babies fed roller process dried milk was closely similar to that of a control group in all the points examined: rate of gain in weight; general resistance to infection; resistance to infections of the mouth, eyes and skin; incidence of noninfective cutaneous lesions, and texture of the skin. The roller process dried milk used supplied, therefore, a sufficient amount of vitamin A to meet the infants' needs. This work does not render negative the author's previous findings, which suggested that roller process dried milk did not fully meet the infants' requirements of vitamin A, as, for reasons stated in the paper, it cannot be affirmed that the vitamin A content of the milk was the same over the two different periods. It is suggested that, pending other investigations on the subject, it is desirable to give artificially fed babies a supplement providing extra vitamin A. KELLY, Milwaukee.

ANTIRACHITIC VALUE OF HUMAN MILK. J. C. DRUMMOND, C. H. GRAY and N. E. G. RICHARDSON, Brit. M. J. **2**:757 (Oct. 14) 1939.

The authors comment on the lack of precise information regarding the antirachitic potency of human milk. A large proportion of the work on this point has been done by experimentation on animals. The calcium requirements of the numerous infants are studied and outlined, as are the factors leading to rickets. Then follows a study of the factors influencing the vitamin D content of milk and the influence of the calcium-phosphorus ratio. The authors conclude that there is need for more information concerning not only the composition but also the yield of milk from mothers whose diet, "adequate in all other respects, provides at least 2 grammes of calcium, 1.5 grammes of phosphorus, and 300 I.U. of vitamin D daily." Thus the authors have given the results of their analysis of human milk for vitamin D, calcium and phosphorus, as well as the correlation between the vitamin D content of the diet and that of the milk.

ROYSTER, University, Va.

PELLAGROID ERYTHEMA AND LAMBLIASIS. A. COPPOLINO, Med. inf., Rome **10**:264 (Sept.) 1939.

A 12 year old boy showed at first gastrointestinal, then cutaneous, symptoms of pellagra. He had anorexia, thirst, poor digestion and diarrhea. There were lesions of the skin on the face, neck, hands and legs, which were erythematous and slightly edematous and had a tendency to desquamate. Lamblia intestinalis was found in large numbers in the stools. The red blood cell count was 2,800,000; the white cell count, 5,000. The hemoglobin content was 85 per cent. Eosinophils numbered 3 per cent of the white cells.

Lamblia infection is not uncommon in pellagrins in Sicily. The vitamin deficiency is not primary but is due to the failure of absorption of vitamin B following infection by these intestinal parasites. HIGGINS, Boston.

VITAMIN $B_1$ METABOLISM OF THE INFANT. F. WIDENBAUER and H. KRUGER, Ztschr. f. Kinderh. **61**:52 (June 6) 1939.

There is a disproportion of the intake and excretion of vitamin B because of synthesis of the vitamin by bacteria in the large intestine. A diet free from vitamin B should therefore precede studies of balance. It was found that arti-

ficially fed infants utilize an average of 16 micrograms of vitamin B per hundred calories of food intake. Since cow's milk contains an average of 50 micrograms of vitamin B per hundred calories, the average artificially fed infant receives the vitamin in adequate amounts. Breast-fed infants utilize much less vitamin B (an average of 9 micrograms per hundred calories) than do artificially fed infants. Possible causes for the difference are discussed. The vitamin B and cocarboxylase content of the stools is approximately the same in artificially and in breast-fed infants, but vitamin B is not absorbed from the large intestine. Fever increases the utilization of vitamin B, and diarrhea interferes with the absorption of it.

SIEMSEN, Chicago.

NATURE OF ANTIRACHITIC VITAMIN IN IRRADIATED MILK. A. FLEISCH, Ztschr. f. Vitaminforsch. **8**:217, 1938.

Irradiated milk contains no vitamin $D_2$ (calciferol); however, another antirachitic substance is present, probably vitamin $D_3$ (7-dehydrocholesterol). In addition to this substance, toxic substances formed during the irradiation are present in irradiated milk, such as lumisterol or tachysterol. Consequently, crystalline vitamin $D_3$ or cod liver oil is to be given preference over irradiated milk.

ARON, Chicago.

VITAMIN C REQUIREMENTS OF PREGNANT AND LACTATING WOMEN. K. UTHEIM-TOVERUD, Ztschr. f. Vitaminforsch. **8**:237, 1938.

A saturation test with 500 cc. of orange juice was performed on each of 8 adult nonpregnant women, 12 pregnant women and 10 lactating women. All women were on a diet containing on an average 30 mg. of ascorbic acid daily. While the 8 normal adult nonpregnant women excreted at least 50 per cent of the test dose during twenty-four hours, the highest excretion in pregnant women was 26 per cent; in lactating women in only a single instance did the excretion exceed 10 per cent of the test dose. A diet supplying 75 mg. of ascorbic acid daily was also not fully sufficient for the pregnant and was insufficient for the lactating women. With a daily intake of 100 mg. of ascorbic acid in addition to the diet supplying 75 mg. of ascorbic acid daily, there was a 50 per cent excretion after from two to three weeks by pregnant women and after from five to eight weeks by lactating women.

During saturation the ascorbic acid in the blood usually rose to a level of 1 mg. per hundred cubic centimeters and higher. The blood showed from 0.6 to 0.8 mg. per hundred cubic centimeters in a few instances in which the urine showed full saturation.

With a daily intake of 75 mg. of ascorbic acid the breast milk showed a low level of ascorbic acid (average for 75 samples, 3.9 mg.). When the daily intake was raised to 100 mg., the content in the breast milk was satisfactory.

The author believes that a latent vitamin C deficiency is frequent in Norway, especially in pregnant and in lactating women. She emphasizes that in stillborn infants hemorrhages are encountered and that the ascorbic acid in the livers of these infants is decidedly low.

ARON, Chicago.

## Hygiene; Growth and Nutrition; Public Health

THE RELATION BETWEEN CHANGE IN BASAL METABOLISM AND GROWTH DURING ADOLESCENCE. C. B. DAVENPORT, O. RENFROE and W. D. HALLOCK, Child Development **10**:181 (Sept.) 1939.

A study was made of the correlation between changes in basal metabolism (percentage departure from standard basal metabolism) and changes in speed of physical growth as observed "longitudinally" for 55 boys and 55 girls over a period of from five to eight years, before, during and after the adolescent spurt of growth.

Mass correlations were mostly low, not over +0.36. Intraindividual correlations varied from —1.00 to +1.00. The averages of such intraindividual correlations were a little higher between basal metabolism and body weight than between basal metabolism and stature. The correlation between excess of body build and excess of oxygen consumption was high for girls (0.483), but not for boys. The highest correlation (0.67) was between basal metabolism and weight among girls whose weight change amounted to a deviation of ±2.5 Kg. per year from expected gains. Thus, during the adolescent spurt of growth the increase in basal metabolic processes associated with increasing weight may amount to 10 per cent or more of the basal metabolism as determined before and after this spurt.

FROM AUTHORS' SUMMARY.

THE CENTER, THE GROUP UNDER OBSERVATION, SOURCES OF INFORMATION, AND STUDIES IN PROGRESS. H. C. STUART and others, Publication 1, Center for Research in Child Health and Development, Harvard School of Public Health. Monograph of the Society for Research in Child Development, Washington, D. C., National Research Council, 1939, vol. 4, no. 1.

In this monograph the staff of the Center for Research in Child Health and Development has attempted to describe the conditions under which their observations were made, the group on which they were made, and the interrelations existing between the various divisions of this research. This general descriptive material will obviate the need for repetitive descriptive material in further reports of particular studies at the center. Research activities at the center fall into the following principal divisions: sociologic, dietary, pediatric, dental, orthopedic, anthropometric, psychometric, other psychologic, roentgenographic and photographic.

Considerable space has been given to the methods used in acquiring children for study and maintaining satisfactory relations with their families, and to changes in procedure which have been made from time to time. This has been done in order to bring out some of the possibilities and limitations inherent in this type of "longitudinal" study of children living in "normal" circumstances.

Part 4 presents the case histories of 2 sisters and their families. This affords an actual example of the kind of information available in the center's case records. It also shows the methods of analysis of these family case records which the staff attempts to use. The graphic method of presentation of normative data and the comparison of the growth of individual subjects with the standards used are given considerable attention in this analysis.

PALMER, Washington, D. C.

TYPES, LEVELS AND IRREGULARITIES OF RESPONSE TO A NURSERY SCHOOL SITUATION OF FORTY CHILDREN OBSERVED WITH SPECIAL REFERENCE TO THE HOME ENVIRONMENT. E. SLATER with the assistance of R. BECKWITH and L. BEHNKE, Publication 2, Center for Research in Child Health and Development, Harvard School of Public Health, Monograph of the Society for Research in Child Development, Washington, D. C., National Research Council, 1939, vol. 4, no. 2.

This monograph is a report of the studies made in the research nursery school at the Center for Research in Child Health and Development. Part 1 describes the 40 children who made up the nursery school group and the general types of information recorded about their behavior. Marked contrasts were observed in the tempo and in the variety of the activities of these children during their first few days in the nursery. Furthermore, there was a striking tendency for children who made a high number of responses at the beginning of the observation period to make a low number before the end of the period, and for those who made few responses in the beginning to follow an opposite trend. These two groups were called "accelerated" and "inhibited," respectively; there were 12 children in the former and 13 in the latter group. Fifteen children did not follow a simple pattern but constantly fluctuated in the tempo of activities. These children are referred to

as "alternating." Tics and dreamy watching occurred most frequently in the "inhibited" and the "alternating" group, while crying was more characteristic of the "accelerated" group. The "inhibited" children rated higher as a group in intelligence, and none of the "accelerated" children were in the highest intelligence group. More "alternating" children had oversolicitous parents or unfavorable health experiences. These findings suggest that there are two or possibly three fundamental patterns which children follow in reactions to new experiences. These classifications are further substantiated by case histories.

Part 2 gives a detailed description of the different responses which were observed in the nursery and presents a classification of "Intellectual, Motor, Social and Emotional Responses." Part 3 is a discussion of the irregularities shown in the behavior of some of these children. Brief case histories of the 13 most irregular children are presented. The changes in the home background and environment which may have accounted for the irregularity in nursery school behavior are discussed. Samples of the record forms used are presented in the appendix.

PALMER, Washington, D. C.

THE PHYSICAL AND MENTAL GROWTH OF GIRLS AND BOYS AGE SIX TO NINETEEN IN RELATION TO AGE AT MAXIMUM GROWTH. F. K. SHUTTLEWORTH, Monograph of the Society for Research in Child Development, Washington, D. C., National Research Council, 1939, vol. 4, no. 3.

This is the third volume by Dr. Shuttleworth on the physical growth of children aged 6 to 19 to be published in the monograph series of the Society for Research in Child Development. The first volume, "Sexual Maturation and the Physical Growth of Girls Age Six to Nineteen," published in 1937 as volume 2, no. 5, serial no. 12, analyzed the growth curves of 248 girls, classified into eight groups according to menarcheal age, in respect to eight physical dimensions, erupted teeth and skeletal ages. The second volume, "Sexual Maturation and the Skeletal Growth of Girls Age Six to Nineteen," published in 1938 as volume 3, no. 5, serial no. 18, analyzed the growth curves of 103 girls, classified into three groups according to menarcheal age, in respect to twelve dimensions derived from roentgenograms. The present volume analyzes the growth curves of 747 girls and 711 boys, classified into nineteen groups according to "MG-age" (i. e., age at the close of the year of maximum increase in standing height), in respect to nine physical dimensions, erupted teeth and intelligence. These "MG-ages" are believed to be symptomatic of age at sexual maturity in both girls and boys; they are highly reliable, and they permit an exact classification of subjects according to the timing of different phases of their growth patterns. The volume includes 110 tables and 152 charts. Most of the 324 charts in the three volumes are drawn according to a uniform plan which facilitates a direct comparison of the growth patterns generated by each of the twenty-two dimensions which were studied. The findings of the three volumes are summarized and interpreted as a unit. Twelve major generalizations are presented. Three types of growth patterns from birth to maturity are distinguished. The nature of these growth patterns is attributed to the progressively changing balance of five underlying factors. The findings and interpretations are not amenable to brief abstracting. The importance of the three volumes may be suggested by quoting an appraisal of the first volume. "It is revolutionary in its methods of analysis, unexcelled for its graphical representations, and monumental in its contributions to new knowledge." The second and third volumes add little to the methodologies of the first, but greatly extend and elaborate both findings and interpretations. The significance of these volumes is enhanced by the fact that the original data, comprising nearly 190,000 measurements collected by the workers employed in the Harvard study of growth, have been published in detail by Dearborn, Rothney and Shuttleworth as volume 3, no. 1, serial no. 14, in the same monograph series.

PALMER, Washington, D. C.

EXERCISE FOR CHILDREN AND ADOLESCENTS. P. NOBÉCOURT, Gaz. d. hôp. **112**:1313 (Oct. 18); 1329 (Oct. 25) 1939.

In the first eighteen months the infant learns how to exercise the muscles which coordinate its movements and maintain its balance. Thus exercise progresses parallel with perfection of the central nervous system and of the organs of locomotion. Before puberty growth is chiefly osseous, afterward muscular, especially in boys. Exercise before puberty ought to be harmonized and not too vigorous. Not until adolescence is exercise involving only a certain group of muscles permissible, because of the danger of unharmonious body development. Exercise ought to be pleasurable and not forced or exaggerated.

Exercise increases the consumption of carbohydrate by the muscles and increases the production of carbon dioxide, which leads to dilatation of the capillaries and an increase in circulation. Repeated exercise increases the muscle volume. The effect of exercise on the rate of respiration and the pulse rate becomes less marked when the same exercise is repeated regularly. Exercise does not influence growth in height. Exercise is important in the building of character. Exercise to excess will cause insomnia, dilatation of the heart, pains in the joints, loss of weight and anemia.

KAJDI, Baltimore.

SOCIAL SERVICE IN RURAL COMMUNITIES. MOUTILLARD, Rev. méd.-sociale et de protec. de l'enf. **7**:197 (May-June) 1939.

This article is a description of social service in a rural community in France by the person in charge of the social welfare work in that community.

The work is done by trained social workers and consists in visiting families of peasants, helping them to settle various problems concerning family relations, housing, economic situation and children's attendance at school. One of the most important functions of social service, in Mlle. Moutillard's opinion, is teaching the peasant proper care of health, particularly of that of the mother and children, and helping him to take measures for the prevention of tuberculosis and various prevalent diseases. [Most of these services are considered functions of public health nurses in the United States.—ABSTRACTER.]

BIERMAN, Washington, D. C.

## Newborn

PAPILLARY TUMOR OF THE CHOROID PLEXUS IN A NEWBORN INFANT. G. A. DRUCKER, Arch. Path. **28**:390 (Sept.) 1939.

Papilloma of the choroid plexus is one of the rarest of cerebral neoplasms. Cushing mentioned 12 in his series of 2,000 intracranial tumors. The tumor reported is the first observed in a newborn infant. A mass, 4 by 3.5 by 3 cm., was found below an atrophic area of the cortex of the left parietal and occipital lobes, within a greatly dilated posterior horn of the left lateral ventricle; it was firmly attached to the floor, medial wall and roof and to the choroid plexus, coming from the inferior horn. The mass was soft, papillary and grayish pink. Histologically, the neoplasm was characterized by branching papillae, each of which consisted of a core of vascularized connective tissue covered by a single layer of tall columnar epithelium.

The previously reported cases of papilloma of the choroid plexus occurring in a young infant are similar in their essential features.

APPELBACH, Chicago.

SOME OBSERVATIONS ON CEREBRAL HEMORRHAGE IN THE NEW-BORN. H. N. SANFORD, Illinois M. J. **76**:162 (Aug.) 1939.

Sanford discusses the causes, diagnosis, differential diagnosis and treatment of cerebral hemorrhage in the newborn. He deplores the general tendency to place the blame on the obstetric care, for probably in less than half of the cases may the

hemorrhage be directly attributed to the management of the delivery. Etiologically, there are two general factors: a strain on the cerebral vessels and some factor that causes a weakening of those vessels. These factors may exist alone but usually occur together.

The diagnosis is exceedingly difficult unless one has absolute proof by autopsy. The three cardinal symptoms are convulsions, cyanosis and flaccidity followed by spasticity. Other signs and symptoms may exist in individual cases but are not of much value in diagnosis. The differential diagnosis rests between other causes of convulsions or spasticity in the newborn and conditions that cause asphyxia and cyanosis.

In the prophylaxis, conservative methods of delivery should result in a diminution of injuries. Since, however, prematurity and illness of the mother during pregnancy are important in the production of cerebral hemorrhages of the newborn, prophylaxis is much more important during pregnancy than in delivery. Every mother should have the benefit of a thorough physical and pelvic examination, and all defects that might interfere with successful labor and the health of the mother and the fetus should be corrected at that time. A nutritious diet, rich in salts and vitamins, should be assured.

As to the treatment of the infant with cerebral hemorrhage, the principal rule is to keep the baby warm and quiet and to handle him as little as possible. The author does not believe in the use of spinal punctures either for diagnostic or for therapeutic purposes; nor does he believe in the injection of blood, as a prophylactic or as an active therapeutic measure, unless the bleeding and coagulation times are increased.

BARBOUR, Peoria, Ill.

VARIOUS COMPLEMENTARY FEEDINGS USED DURING THE NEONATAL PERIOD. H. N. SANFORD, J. A. M. A. **113**:470 (Aug. 5) 1939.

Over a period of nine years more than 4,000 babies were observed during the newborn period when they were fed by different technics. Sanford compares the weight lost, the weight regained and the stimulation of breast secretion of milk when protein milk, lactic acid milk or whole milk formulas were used, when 5 per cent carbohydrate plus breast milk was used, and when breast feedings were given with only water in addition. One third of these babies lost 5 to 8 per cent of their birth weight, but of those given high caloric feedings besides the breast milk one half lost 5 per cent or less. More of those fed additional food regained their birth weight in ten days. Actually the gain is faster in babies that are entirely breast fed, owing to the greater initial loss.

The most significant finding was the suppression of secretion of mother's milk when feedings high in calories were given. Fifty-three per cent of babies given no complementary feedings and nursed six times a day, and 41 per cent of those fed only the breast milk five times a day, were receiving sufficient breast milk on discharge.

HEERSMA, Kalamazoo, Mich.

ANEMIA OF THE NEWBORN. P. COHEN and L. M. SHAPIRO, M. Clin. North America **23**:581 (May) 1939.

Anemia of the newborn is but one expression of a disease process called erythroblastosis foetalis. The related entities are the Schridde type of congenital hydrops and icterus gravis neonatorum. The underlying pathologic change is a widespread extramedullary hemopoiesis, occurring especially in the liver and spleen. Erythroblastemia may or may not be present in any of these conditions and is usually absent in congenital anemia. Anemia of the newborn may occur as a sequel of universal edema of the newborn or of icterus gravis neonatorum or as "pure" anemia, with or without jaundice. Few infants with universal edema of the newborn survive. If a child with icterus gravis survives, the anemia which

emerges assumes the characteristics of congenital anemia. In jaundiced infants the presence of anemia may not be suspected. The occurrence of deep yellow amniotic fluid and vernix caseosa should arouse a strong suspicion of the presence of erythroblastosis foetalis.

The prognosis in cases of "pure" congenital anemia is quite favorable. The only measure of definite value in treatment is transfusion, especially if icterus gravis is suspected. However, the indications for this measure should be the general condition of the patient rather than the blood picture alone. Too many transfusions may increase the hemolysis.

EUGENE H. SMITH, Ogden, Utah.

EPIDEMIC DIARRHEA OF THE NEWBORN—A NEW DISEASE? S. FRANT and H. ABRAMSON, New York State J. Med. **39**:784 (April 15) 1939.

The following table contains a summary of 27 outbreaks of epidemic diarrhea of the newborn in New York between July 1934 and December 1937.

| | |
|---|---|
| Total number of exposed liveborn babies | 5,082 |
| Total number of babies attacked | 750 |
| Morbidity rate | 14.7% |
| Total number of deaths | 356 |
| Mortality rate | 7.0% |
| Case fatality rate | 47.5% |

Those dealing with this epidemic in New York feel that this disease is a newly recognized syndrome, different from the general diarrheal disorders of infancy. It is limited to infants in the first month of life, and while it is highly virulent and communicable among the newborn, it does not spread to older children or to adults caring for sick babies. A study shows that the period of incubation is about six days. During the stage of invasion the illness may be mild for a day or two, with loss in weight, anorexia, drowsiness, vomiting, distention and moderate diarrhea. There is usually little fever. The condition is easily mistaken for diarrhea due to faulty feeding. It is while the disease is thus unrecognized that it spreads to other infants in the ward. In a few days the disease becomes more acute, and the child becomes toxic. The stools are numerous, watery, yellow and fairly free of mucus, blood or pus. Abdominal distention increases. Dulness, dehydration, toxicity and shock complete the picture. Except for detecting low levels of carbon dioxide in the blood, laboratory investigations are of little value. On the average, death occurs in about seven days. The causative agent has not yet been determined. In order to control this disease, an amendment to the sanitary code of the city makes "diarrhea in the newborn up to three weeks of age occurring in a hospital giving maternity service" a reportable disease. This amendment placed under the jurisdiction of the Bureau of Preventable Diseases all infants with diarrhea which might possibly be of the epidemic type, and "allowed us to enforce stringent isolation and quarantine measures similar to those used in the control of any other communicable condition." A study was made of deaths in babies under 1 year of age and of deaths occurring in the newly born. It was found that it was necessary to have certain minimal requirements for nurseries of the newborn. Strict surgical asepsis is the basis used in establishing proper care of the newborn. Maternity services are made as self contained as possible. Separate nurseries are provided for full term and premature babies, also isolation facilities for sick children. The formula room and its staff, together with the nursing personnel on duty, are kept from contact with the rest of the hospital.

AIKMAN, Rochester, N. Y.

DIAGNOSIS OF SYPHILIS IN THE NEONATAL PERIOD. M. L. BRIDGEMAN, Northwest Med. **38**:389 (Oct.) 1939.

To establish the diagnosis of neonatal syphilis one has to depend on (1) clinical evidence, (2) the results of a pathologic examination of the placenta and umbilical cord, (3) serologic tests of the parents and of the baby and (4) roentgenograms of the bones of the infant.

A difficult question comes to the doctor when the baby shows no evidence of syphilis clinically but the Wassermann test of blood from the umbilical cord is positive. It is the feeling of the author that every child indicated as having syphilis by a 4 plus Wassermann reaction of blood from the umbilical cord should have repeated serologic tests and be followed with roentgenograms of the long bones until the presence or absence of active syphilis is proved.

ROBERTSON, Omaha.

ACUTE OTITIS MEDIA IN THE NEWBORN. L. A. PARSELL, Northwest Med. **38**:471 (Dec.) 1939.

Four cases of otitis media occurring in the newborn are reported. In each case myringotomy was performed, with relief of symptoms but with little drainage. In 1 case the tonsils and adenoids were removed at the age of 6 months.

ROBERTSON, Omaha.

SPONTANEOUS MUTILATING GANGRENE OF THE FINGERS OF AN INFANT. J. HUBER, J. FLORAND and M. PAYET, Bull. Soc. pédiat. de Paris **37**:54 (Feb.) 1939.

An infant 3 weeks old was admitted to the hospital because of diarrhea and fever. He was dehydrated and was given fluid by hypodermoclysis, intraperitoneally and by intravenous continuous drip. He made a good recovery, but it was noticed that the lower parts of the fingers had become cyanosed. A few days later there was dry gangrene of the tips of several fingers, the nails of which were shed. The terminal phalanx of the right index finger was completely gangrenous. A satisfactory explanation of this complication was not found.

BENJAMIN, Montreal, Canada.

POSSIBILITY OF A HEREDITARY PREDISPOSITION IN ADIPONECROSIS. G. PANCALDI, Pediatria **47**:413 (May) 1939.

Pancaldi describes a case in which, after a difficult labor, adiponecrosis developed in a newborn infant. In the left cheek there was a small round mass the size of a hazelnut. It was adherent to the skin but movable on the underlying tissues. In the mammary regions there were two similar masses, about 3 cm. in diameter. Several masses were located on the back and on the upper and lower parts of the right and left arms. Microscopic and histologic examination showed that all these masses were constituted of fat. A similar lesion occurred in the father after he had received antityphoid vaccination, when he was in the army. The fact that a similar lesion of adiponecrosis occurred in the father leads the author to conclude that there is a hereditary constitutional factor in adiponecrosis.

MARTOCCIO, Utica, N. Y.

SOUR MILK AS A FEEDING FOR THE NEWBORN. W. MALZ, Monatschr. f. Kinderh. **79**:323, 1939.

In the absence of human milk, Malz prescribed whole cow's milk acidified with lemon juice for feeding the newborn. The results were satisfactory.

GERSTLEY, Chicago.

PATHOGENESIS OF MELENA NEONATORUM. H. WINKLER, München. med. Wchnschr. **85**:476 (March 31) 1938.

Melena neonatorum is more frequent during the winter than during the summer. Of the 12 cases observed by Winkler, only 2 occurred in the summer. Both mothers in these 2 instances had been in dire circumstances, subsisting on bread, potatoes and skim milk. This fact led to the idea that the melena neonatorum was the result of a deficiency of vitamin C.

A 35 year old mother became pregnant for the fifth time in seven years. During the second half of her pregnancy, scurvy developed, for which she was treated with ascorbic acid. She delivered a boy 53 cm. long and weighing 4,250 Gm. On the second day there were bloody watery stools. For the next three days there were eight bloody stools daily. One hundred milligrams of ascorbic acid was given intramuscularly daily, and on the fifth day the bleeding stopped. Eight days passed before 60 per cent of the ascorbic acid was recovered in the urine. This delay indicated that there was a marked deficiency of vitamin C.

Winkler studied the excretion of ascorbic acid in the milk. The ascorbic acid in the milk of the mother was between 2 and 3 mg. per hundred cubic centimeters for eight days. Then 300 mg. of ascorbic acid was given intramuscularly each day. Two and four days later the value was 4, and it rose to 8 on the sixth day. There was a corresponding lag in the urinary excretion of ascorbic acid.

BRAHDY, Mount Vernon, N. Y.

DELAYED CEREBRAL HEMORRHAGE IN NEWBORN INFANTS. L. SALOMONSEN, Acta pædiat. **24**:442, 1939.

According to Salomonsen, the concept of hemorrhagic disease of the newborn is not so well recognized in Europe as in America. For this reason that condition is usually ignored as a possible cause of the cerebral hemorrhage which does not become manifest until the third day of life or later. Such a hemorrhage is usually ascribed to reactivation of an intrapartum hemorrhage as the result of crying, rather than to a general tendency toward hemorrhage.

The author's argument consists of two parts: First, daily measurements of bleeding time in 100 infants during the first ten days of life revealed a prolongation from 4.4 minutes on the day of birth to 5.7 minutes on the third day, then a decline to 4.0 minutes on the ninth day. Second, no evidence of hemorrhagic diathesis was discovered in 70 infants with intracranial hemorrhage that became manifest within forty-eight hours after birth. On the other hand, of 19 infants that gave no symptoms until after the end of the second day of life, signs of a general tendency to bleed were found in 13. This evidence included actual bleeding into or from the skin or mucous membranes, or a markedly prolonged bleeding time. Prompt transfusion is recommended in all cases of intracranial hemorrhage with delayed manifestations.

McCUNE, New York.

## Acute Contagious Diseases

INCLUSION BODIES IN SCARLET FEVER. J. BROADHURST, G. CAMERON, M. E. MACLEAN and V. SAURINO, J. Infect. Dis. **64**:193 (May-June) 1939.

About the time that every one has come to believe that scarlet fever is due to streptococci, these authors conclude that it may be due to a virus, because in scarlet fever they found inclusion bodies present in the tissues of the upper respiratory tract, in the white blood corpuscles, and in serial tissue cultures inoculated with bacteria-free filtrates of the blood of patients.

TOOMEY, Cleveland.

USE OF GASTRIC MUCIN IN THE DIAGNOSIS OF EPIDEMIC MENINGITIS. S. E. SULKIN, J. Infect. Dis. **64**:210 (May-June) 1939.

Sulkin confirms the observations on Miller's mucin-mouse method. When the sediment from a spinal fluid containing meningococci is combined with mucin

and injected intraperitoneally, the meningococci are easily found in the peritoneal exudate. The conclusion might be drawn that this method is superior to direct microscopic and cultural methods of diagnosing meningococcic meningitis.

TOOMEY, Cleveland.

ACTIVE AND PASSIVE IMMUNIZATION IN EXPERIMENTAL POLIOMYELITIS. F. B. GORDON, P. HUDSON and J. A. HARRISON, J. Infect. Dis. **64**:241 (May-June) 1939.

These authors tried to produce active immunity, and to demonstrate the effect of passive immunity, in monkeys. To establish active immunity they used crude virus, preparations of virus in gelatin containing aluminum, and an eluate and found by the neutralization test that there was no evidence to demonstrate that any one of the three antigens was superior or produced a better immunologic response in monkeys. They injected crude virus and a preparation of virus in gelatin containing aluminum into sheep and thought that they obtained a greater antibody response than might be expected with crude virus alone. They were not able to demonstrate any resistance in animals which had been immunized with antigen made of crude virus or with a preparation of virus in gelatin containing aluminum, injected subcutaneously, for the animals became ill when given the disease by the intranasal route. Passive immunity produced by using large amounts of blood from convalescent and hyperimmunized monkeys failed to protect animals when virus was subsequently introduced intranasally.

TOOMEY, Cleveland.

MODERN CONCEPTS IN MEALES CONTROL. A. WEINZIRL, Northwest Med. **38**:170 (May) 1939.

Outbreaks of measles cannot be cut short by any means now available. During an outbreak good medical and nursing care are of paramount importance. The use of convalescent serum or of immune globulin in patients with severe measles warrants consideration. These agents are also indicated in the treatment of "poor measles risks" who are known to have been exposed.

The attitude that public health and visiting nurses should not go into families where there is measles should be abandoned.

ROBERTSON, Omaha.

PREVALENCE OF POLIOMYELITIS IN THE UNITED STATES IN 1938. Pub. Health Rep. **54**:857 (May 26) 1939.

The number of cases of poliomyelitis reported in 1938 was lower than that in any year since 1916. The incidence was at a fairly low endemic level in all sections of the country. For one state, Nevada, no cases were reported, and for New Hampshire and Wyoming 1 case each was reported. The highest rates of incidence were reported in the District of Columbia (4.3 per hundred thousand) and South Dakota (4.0). There were no outstanding advancements in the epidemiology of poliomyelitis during the year. Progress in this field now depends on finding more suitable, i. e., more susceptible animals for experimental investigations than those available at the present time.

SANFORD, Chicago.

CLINICAL EXPERIENCES IN THE TREATMENT OF MENINGOCOCCEMIA AND MENINGOCOCCIC MENINGITIS. W. A. CLYDE and M. G. NEELY, South. M. J. **32**:594 (June) 1939.

Clyde and Neely feel that antitoxin should be given all children with meningococcic infections who are acutely toxic and that it should be given within the first twenty-four to forty-eight hours. At the same time sulfanilamide therapy should be started and continued for eight to twelve days, or longer if necessary.

They believe that antitoxin may be given in slightly smaller amounts when used in conjunction with this drug. In highly allergic persons, they feel justified in using the chemical alone. In patients seen late, in whom the normal secretion and absorption of the spinal fluid might be interfered with, it may be wise to give sulfanilamide solution intrathecally. They feel that the administration of antitoxin intrathecally is unwise, not necessary and possibly harmful. They state that the most dramatic results have been obtained by the use of antitoxin by vein plus sulfanilamide therapy and without frequent spinal punctures.

With many of their patients, they felt sure that they had not given sufficient amounts of antitoxin. They also gave sulfanilamide in smaller doses than are commonly used. They did not give sodium bicarbonate grain for grain with sulfanilamide as recommended by most clinicians.

In a few of their patients a slightly cyanotic appearance developed while sulfanilamide was being taken, and in an infant severe anemia developed, but otherwise they were fortunate in not having rashes or other signs of sensitivity to the drug.

Their highest mortality occurred in children treated with antitoxin only and intravenously only. However, they felt that the high rate was due partly to the age and type of condition and partly to an insufficient initial dose of antitoxin.

The spinal fluid cell count apparently has no direct relation to the toxic symptoms seen or to the prognosis or the rapidity of recovery, but it probably has some relation to the development of sequelae.

As to prognosis, continued coma or stupor in spite of treatment is a bad sign. Return of mental alertness and return of appetite are always good indications. In many of the cases encephalitis is present as well as meningitis. In such cases several months may elapse before a return to normal may be expected.

SCHLUTZ, Chicago.

HOSPITAL EXPOSURE TO THE COMMON CONTAGIOUS DISEASES OF CHILDREN. F. C. NEFF, South. M. J. **32**:623 (June) 1939.

Neff believes that an ideal construction for children exposed to common contagious diseases would be the building of small rooms exclusively, doing away with wards.

Every effort should be made to detect the presence of contagion in visitors, prospective patients and the hospital personnel. Only immune nurses should be assigned to children's wards. It should be the duty of some one of the personnel to watch daily throughout the hospital for early signs of contagion. Active immunization should be performed on children who are to stay in the hospital for any extended period. Passive immunization should be given hospital children in the presence of a case of active infection or an epidemic.

SCHLUTZ, Chicago.

ADULT SERUM IN A SCHOOL EPIDEMIC OF MEASLES. L. R. LEMPRIERE, Brit. M. J. **1**:1136 (June 3) 1939.

Lempriere reports the use of adults' serum in combating an epidemic of measles in public schools generally and particularly at Haileyburg College. The work was controlled in a measure, and the complications were calculated in both the treated group and the control group. The author concludes that the results as they appear on paper seem rather poor, but he is convinced that many factors enter into the problem and that the use of such serum is a good procedure. The epidemic was more free from complications and anxieties than usual. The two groups are compared as to height and duration of fever, degree of illness and incidence of complications.

ROYSTER, University, Va.

POTASSIUM TELLURITE IN THE DIAGNOSIS OF DIPHTHERIA. E. TOMLIN, Brit. M. J. **1**:1273 (June 24) 1939.

This test for diphtheria is made by applying a 2 per cent solution of potassium tellurite in distilled water. The solution must not be heated above 40 C. It loses its efficiency after a month. The solution is applied to exudative throats by means of a swab. In the original experiment by Manzullo the reaction was read in from five to ten minutes. Tomlin thinks that a longer time should be allowed, say from fifteen to thirty minutes. If the exudate is darkened by the tellurite, the assumption is that it is diphtheritic. If no darkening occurs, it is assumed that the exudate is nondiphtheritic. The negative result, the author feels, is practically 100 per cent diagnostic. When darkening occurs, he does not rely on it to the same extent, because false darkening can occur. When the result is thus positive, it is still necessary to do a bacteriologic study. ROYSTER, University, Va.

IMMEDIATE TELLURITE TEST IN DIPHTHERIA. J. B. L. TOMBLESON and R. M. CAMPBELL, Brit. M. J. **1**:1275 (June 24) 1939.

The tellurite test was applied in 200 cases of pharyngeal infection. The authors conclude that a negative finding, i. e., no discoloration or darkening after the application of the tellurite solution, is presumptive evidence that the condition is not diphtheria, but that a positive finding does not establish such a diagnosis.

ROYSTER, University, Va.

THREE CASES OF CEREBROSPINAL FEVER TREATED BY M & B 693. W. H. OSBORN, Brit. M. J. **1**:1281 (June 24) 1939.

Three patients with cerebrospinal meningitis were given sulfapyridine (2-[para-aminobenzenesulfonamido]-pyridine; preparation used, M & B 693) by daily lumbar punctures. All responded promptly to the therapy and recovered.

ROYSTER, University, Va.

TREATMENT OF SCARLET FEVER. H. S. BANKS, Practitioner **142**:693 (June) 1939.

Banks summarizes his points as follows: 1. The scarlet fever syndrome is an inconstant accompaniment of infection with a hemolytic streptococcus. 2. Problems of infectivity and isolation should be considered in relation to the whole group of hemolytic streptococcic infections. 3. Antitoxin is the best means of treatment. It should be given to all but those whose illness is of the mildest type. It may be combined with chemotherapy to reduce septic complications. 4. The period of isolation in the hospital should be short. 5. Prophylactic immunization has many disadvantages but occasionally has value. GELSTON, San Francisco.

TREATMENT OF DIPHTHERIA. C. J. MCSWEENEY, Practitioner **142**:701 (June) 1939.

It is rather anomalous that in 1939 it should still be necessary to include in a symposium the treatment of a disease which is now completely preventable, for in communities enlightened enough to practice specific immunization on a large scale diphtheria has been eradicated. It is to be hoped that this happy state of things will also come to pass in the British dominions before the lapse of another decade.

The first and most urgent requirement in treating a patient with diphtheria is the administration of diphtheria antitoxin. Speed in this connection is of the greatest importance, the percentage of patients dying from the disease being progressively doubled for every twenty-four hours' delay.

Other treatment discussed includes general supportive measures and management of early and late heart failure, paralysis, laryngeal types of the disease and the carrier state. GELSTON, San Francisco.

EVOLUTION OF SCARLET FEVER IN CHILDREN UNDER TWO YEARS OF AGE. A. STROÈ, H. LAZARESCO-BACALOGLU and I. SCHWARTZ, Arch. de méd. d. enf. **42**:271 (May) 1939.

It has commonly been noted in standard works on contagious diseases that infants up to 6 months enjoy a relative immunity to scarlet fever and that, with few exceptions, severe invasions of this disease are rare before the age of 2 years. Johannessen, however, has reported a mortality rate of 9.9 per cent within this period.

The authors, reviewing recent epidemics in Bucarest, have found an increasing incidence of scarlatina in these younger subjects—in 5,248 children beyond 2 years and in 534 children below this age. All of these children were treated in the pavilions for patients with contagious diseases of the Colentina Hospital. The series was divided into two categories, benign and malignant, and each of these groups was further subdivided into two types according to severity and complications.

Of the 534 young children found infected, there was severe angina in 26 per cent, as compared with a ratio of 13 per cent among the older children. Serotherapy was also less satisfactory in the former class, probably on account of lowered resistance.

AMESSE, Denver.

POSTDIPHTHERITIC PARALYSIS AND SERUM THERAPY. F. CHIUSSI, Lattante **10**:187 (May) 1939.

Chiussi reports 14 cases in which postdiphtheritic paralysis was treated with large doses of antitoxin (80,000 units or more) and believes such treatment shortened the duration of the paralysis. Most of the patients were still carriers of diphtheria bacilli.

HIGGINS, Boston.

ANTIVIRUS THERAPY IN THE DIPHTHERIA OF CHILDHOOD. J. BONABA, R. ETCHELAR and O. MACCIO, Arch. de pediat. d. Uruguay **9**:717 (Dec.) 1938.

Antivirus therapy was used in 25 cases of diphtheria of varying degree of severity. All the patients were treated by local application of the antivirus, according to a method advocated by Claveaux. Good results were obtained in the benign forms. The results in the more severe types were not impressive. All of these types required the additional use of antitoxin. The diphtheria antivirus is not particularly effective in clearing the throats of diphtheria carriers.

SCHLUTZ, Chicago.

VARICELLA ENCEPHALITIS. A. CARRAU and M. E. MANTERO, Arch. de pediat. d. Uruguay **9**:739 (Dec.) 1938.

Varicella encephalitis was observed in a child 8 years old. Cerebellar ataxia developed during the height of the varicella attack. The child's recovery was rapid. The only residual symptoms were diminished reflexes and minor incoordination.

SCHLUTZ, Chicago.

FATAL MENINGOENCEPHALITIS IN A CASE OF MUMPS. VOLPE, Arch. de pediat. d. Uruguay **10**:406 (July) 1939.

Meningoencephalitis occurred in a 7 year old child suffering from mumps localized on the left side. The complication developed on the fifth day and was localized mostly on the right side. Convulsions preceded death. The spinal fluid showed a count of 64 lymphocytes. Volpe believes that the mumps virus was responsible for the development of the meningoencephalitis.

SCHLUTZ, Chicago.

CONGENITAL WHOOPING COUGH. W. MITTELSTAEDT, Kinderärztl. Praxis **10**:270 (June) 1939.

The mother contracted pertussis from one of her children two months before she gave birth to the patient. She apparently did not cough any more after the baby was born. The newborn boy had one attack of asphyxia on the first day of life. He began to cough when he was 7 days old. By the ninth day serious typical pertussis had developed, from which he ultimately recovered.

HEYMANN, Cleveland.

OBSERVATIONS ON DIPHTHERIA. H. OTTO and H. W. HASEMEYER, Monatschr. f. Kinderh. **78**:152 (May) 1939.

Otto and Hasemeyer investigated the types of diphtheria bacilli found in various clinical patients. No one of the three types identified is responsible for any particular clinical entity; in fact, mixed infections are common, and all three types of the organism may be found in the same patient. In one epidemic type III seemed the most virulent.

GERSTLEY, Chicago.

CARBOHYDRATE METABOLISM OF THE HEART MUSCLE IN GUINEA PIGS INFECTED WITH DIPHTHERIA BACILLI AND POISONED WITH DIPHTHERIA TOXIN. H. SCHUMANN, Ztschr. f. d. ges. exper. Med. **105**:14 (Feb. 18) 1939.

One group of guinea pigs was given large doses of diphtheria toxin; another group was infected with diphtheria bacilli. As long as the animals of both groups were in fairly good health, the glycogen content of the heart muscle was found to be higher than in the normal control group. In the ultimate stage, however, a pronounced decrease of the glycogen content of the heart muscle was noticed.

When diphtheria toxin is added to ground muscle, it does not interfere with the phosphorylation of the carbohydrates. It is assumed that the death of the tissues in diphtheria is not caused by these disturbances of the energy metabolism.

ARON, Chicago.

EPIDEMIOLOGY OF SCARLET FEVER. H. M. BROUWER-FROMMANN, Maandschr. v. kindergeneesk. **8**:393 (July) 1939.

The infection which in children of 1 to 3 years was diagnosed as scarlet fever manifested itself in children up to 1 year of age as a commonplace involvement of the nose and throat. Children of 1 to 3 years are relatively more sensitive to scarlet fever than older ones, as "silent" immunization is still absent, and this sensitivity runs parallel to the results of the Dick test at these ages, so that when the opportunity to contract scarlet fever is great, 77 per cent of the children of 1 to 3 years will have the disease. This endemic situation should be considered as an argument for immunizing children from the age of 10 months on against scarlet fever, when necessary, because of their greater sensitivity and the large risk of complications in the very young child.

VAN CREVELD, Amsterdam, Netherlands.

SO-CALLED MORBILLI BULLOSI. J. L. KEYZER, Maandschr. v. kindergeneesk. **8**:437 (Aug.) 1939.

A boy of 8 years was admitted to the hospital with conjunctivitis and a bullous exanthem resembling measles. The skin of nearly the whole body was scaling, and cutaneous emphysema was present on the neck, breast and abdomen. The child died sixty hours later. Neither the five other children of the same family nor any other child in the hamlet where they were living had measles. Moreover, other objections can be raised against the diagnosis morbilli bullosi, as found in the case of Morton (1921). In the author's opinion three types should be dis-

tinguished: (1) real morbilli bullosi, (2) measles complicated by pemphigus and (3) pemphigus morbilliforme acutis gravis, which was the type observed in Morton's case and in this one.

VAN CREVELD, Amsterdam, Netherlands.

ERYTHEMA GLUTAEALE VACCINATUM. J. L. KEYZER, Maandschr. v. kindergeneesk. **8**:474 (Sept.) 1939.

On the buttocks of a child of 6 months without any eczema, small vesicles appeared, greatly resembling those in smallpox. Two days earlier the mother, with her baby, had paid a visit to a house where a young child had been vaccinated eight days before. The diagnosis erythema glutaeale vaccinatum was confirmed by Paul's method, which demonstrated the presence of paranuclear corpuscles of Guarnieri in the cornea of an inoculated rabbit. The "vaccina inoculata" of this child was nearly over when thoracic pneumococci empyema developed, with a swift lethal course.

VAN CREVELD, Amsterdam, Netherlands.

TUSSIS QUINTA AND ALTITUDE FLIGHTS. H. BROEKEMA, Maandschr. v. kindergeneesk. **8**:479 (Sept.) 1939.

The influence of one or two altitude flights on the clinical course of whooping cough was examined in 6 children of 3 years and younger. No definite improvement was obtained in any of them. In 1 case whooping cough bacilli were cultivated after the flight. A 2 year old boy complained of earache on descent, and an infant revealed irregularity of pulse and respiration at an altitude of 3,000 meters. Slight leukocytosis was usually observed during the flight.

VAN CREVELD, Amsterdam, Netherlands.

TREATMENT OF MENINGOCOCCIC MENINGITIS IN BABIES. J. VAN LOOKEREN CAMPAGNE, Nederl. tijdschr. v. geneesk. **83**:2342 (May 20) 1939.

The results obtained with orally administered sulfanilamide and intravenously or intramuscularly injected serum in meningococcic meningitis in 7 infants below the age of 2 years are reported. This report is preliminary, but the results are considered to be very satisfactory with regard to the duration and to the lethality of the disease.

VAN CREVELD, Amsterdam, Netherlands.

## Acute Infectious Diseases

ACTIVE IMMUNIZATION AGAINST TETANUS. H. GOLD, Ann. Int. Med. **13**:768 (Nov.) 1939.

Two injections of alum-precipitated toxoid were found to produce a higher antitoxin titer than three injections of plain toxoid. A "repeat," or stimulating, dose of toxoid is necessary, following the basic course of immunization. The "repeat" dose will increase the antitoxin in the blood of a previously immunized subject to a protective level of 0.1 unit or more within four to six days.

READING, Galveston, Texas.

EPIDEMIC INFLUENZA: STUDIES IN CLINICAL EPIDEMIOLOGY. T. FRANCIS JR., Ann. Int. Med. **13**:915 (Dec.) 1939.

Influenza is an entity. It is caused by a filtrable virus having an affinity for the respiratory tract. A definite antibody response follows an attack. This response can be measured as accurately as that occurring in a bacterial disease. By such means of diagnosis it can be determined that all the epidemics of infections of the respiratory tract which occur from year to year are not epidemics of influenza.

READING, Galveston, Texas.

ROCKY MOUNTAIN SPOTTED FEVER ON LONG ISLAND. Health News **16**:213 (Dec. 25) 1939.

Eight cases of Rocky Mountain spotted fever were found on Long Island during the spring and summer of 1939. One patient was a boy aged 16. A history of tick bites was obtained in all cases but 1. The infection proved fatal in 2 of the 8 cases.

AIKMAN, Rochester, N. Y.

WEIL'S DISEASE: REPORT OF A CASE OCCURRING IN A CHILD. E. E. MARTMER, J. Pediat. **14**:48 (Jan.) 1939.

A three year old white boy had fever, jaundice of hemolytic origin, drowsiness and finally coma. Two weeks prior to the onset of the illness, his pet dog, a Scottie, had become ill with vomiting, fever and jaundice but had recovered. Seventeen days after the onset of the illness the child died. Examination of the blood of a guinea pig inoculated with samples of the child's blood and urine revealed spirochetes. Samples of blood from both the dog and the child were sent to the National Institute of Health, and agglutinations of 1 to 30,000 against Leptospira icterohaemorrhagiae were reported. Tissues removed from the child at postmortem examination were inoculated into guinea pigs and produced jaundice on the second passage. Spirochetes were found in the urine of the guinea pigs dying of jaundice. Sections of liver tissue showed spirochetes on microscopic examination.

This case is of interest not only because of the rarity of the disease but because the source of infection (the pet dog) was definitely proved. Martmer states that specific serum therapy is reported to give encouraging results and may be obtained from the National Institute of Health.

RAUH, Cincinnati.

NEWER CONCEPTS OF BACILLARY DYSENTERY AND OTHER TYPES OF INTESTINAL INFECTION. J. FELSEN, New York State J. Med. **39**:1526 (Aug. 15) 1939.

By more careful bacteriologic, pathologic and clinical investigations, diarrhea can now be more accurately diagnosed. Intestinal infections are divided into two great classes: (1) those due to organisms or toxins originating within the bowel and (2) those that represent local manifestations of systemic diseases. Dysentery, typhoid and Salmonella and staphylococcus infections are included in the first group.

Dysentery presents a great problem in diagnosis in that it is similar to so many other diseases. Any patient with diarrhea should be isolated at once until at least three fecal cultures have been obtained on successive days. This is especially true in institutions, where every effort should be made to determine the source and the type of infection.

In large institutions a trained epidemiologist should be available to prevent and to trace outbreaks by constant supervision of food handlers and other attendants.

In regard to the treatment of bacillary dysentery, Felsen states that serum is of value chiefly within the first twenty-four to forty-eight hours. If serum is not available, whole immune blood may be used. He then suggests the usual type of treatment, especially the RBT (rice-banana-tea) diet supplemented with egg albumin water.

AIKMAN, Rochester, N. Y.

VACCINA THERAPY IN THE RHEUMATIC PATIENT. H. WEINER, New York State J. Med. **39**:1786 (Sept. 15) 1939.

Vaccines have a limited value in the treatment of rheumatism. Responses to vaccine treatment alone are slight, variable and transient. The best results are obtained when sedimentation shows a high index. When the index is normal or only slightly raised, the effects from vaccines are negligible.

AIKMAN, Rochester, N. Y.

ACUTE RHEUMATIC FEVER IN CHILDREN. A. WALLGREN, Irish J. M. Sc., November 1939, p. 793.

This excellent article does not lend itself to abstracting. Any one interested can read the original with profit. SNELLING, Toronto, Canada.

AORTIC ENDOCARDITIS AND ACUTE AORTITIS OCCURRING IN THE COURSE OF AN ATTACK OF ACUTE RHEUMATIC FEVER. P. NOBÉCOURT, Progrès méd. **67**:380 (March 18) 1939.

The child presented in this lecture had his first attack of rheumatic fever at 7 years of age, at which time he was found to have myocarditis and mitral endocarditis. His second attack occurred at the age of 9, and at this time there were, in addition, aortic regurgitation and aortitis as shown by widening of the aortic shadow in the roentgenogram. Nobécourt details other cases in which he has demonstrated aortitis and points out that rheumatic fever is almost as frequent a cause of aneurysm of the aorta in children as is congenital syphilis.

LESLIE, Evanston, Ill.

INTESTINAL ABSORPTION IN CHILDREN INFECTED WITH GIARDIAS. P. VÉGHELYI, Orvosi hetil. **83**:183 (Feb. 25) 1939.

Véghelyi examined the utilization of fat in children infected with Giardia lamblia flagellata and found that the digestion of fat is good but that the digested fat cannot be normally absorbed. The obstacle to normal absorption is the impenetrable layer of protozoa which covers the walls of the intestines. The coloring matter of the urine is also diminished. After treatment the absorption of fat becomes normal; also, the coloring material of the urine.

GÖTTCHE, Budapest, Hungary.

PSITTACOSIS DISCOVERED IN AMSTERDAM BY MEANS OF THE COMPLEMENT FIXATION TEST. A. C. RUYS, A. L. NOORDAM and H. VERVOORT, Nederl. tijdschr. v. geneesk. **83**:3776 (July 29) 1939.

In the last year, apart from a few sporadic cases of psittacosis in a number of families in Amsterdam, after contact with a batch of birds from Helmond, Holland, cases were seen of an illness resembling more or less severe influenza. One of the patients suffered from pneumonia. The complement fixation test, carried out by Bedson's method, confirmed the presumption that these were cases of psittacosis. Probably another batch of birds in Amsterdam was also infected. The virus was isolated from 3 birds (a budgereegah, a ricebird and a gold starling). Only once was more than one person in the same family infected. In 1 case transmission from man to man was probable. In 1 case the complement fixation test was still found strongly positive five years after recovery from the disease.

VAN CREVELD, Amsterdam, Netherlands.

## Chronic Infectious Diseases

THE LARYNX OF THE TUBERCULOUS CHILD. H. RUBIN and S. GALBURT, Arch. Otolaryng. **30**:421 (Sept.) 1939.

Rubin and Galburt discuss the reasons for the infrequency of tuberculous involvement of the larynx in children, such as the protective influence of the lymphatic ring; on the other hand, it may not be observed owing to the mildness of the symptoms or because of seemingly more important complications. Postmortem evidence of its incidence is generally unreliable, for frequently there is a hematogenous spreading of the disease to the larynx or other viscera just prior to death. The manner of infection is discussed. Involvement of the larynx by direct contact with infected sputum is reported as the most frequent mode of

infection. Bronchoscopic examination, vocal rest and application of the galvanocautery electrode are presented as the chief therapeutic measures.

GREENWOOD, Chicago.

EXPERIMENTAL SYPHILITIC KERATITIS IN THE RABBIT. II. A. J. GELARIE, J. Infect. Dis. **65**:84 (July-Aug.) 1939.

Gelarie experimented on a series of syphilitic rabbits. He presents the following summary:

"From the standpoint of pathogenesis there is a marked difference between the primary and metastatic keratitis in experimental syphilis of the rabbit. The latter corresponds to the usual form of keratitis in man and may be considered as a late or tertiary lesion developing as a response of the allergic tissue to the presence of small numbers of spirochetes; which fail to be detected by microscopical or biological methods.

"By serial passages from cornea to cornea, a considerable adaptation of the spirochetes to the corneal tissue can be obtained."

TOOMEY, Cleveland.

CONGENITAL SYPHILIS: A TEN-YEAR STUDY OF FORTY-FIVE CHILDREN. P. J. HOWARD, J. Pediat. **14**:220 (Feb.) 1939.

Forty-five children with congenital syphilis were studied for ten years with final clinically satisfactory results in 85 per cent of the patients. In early infancy the first course of neoarsphenamine should be preceded by injection of a 10 per cent solution of dextrose to protect the liver and to counteract the toxic effects. Complete serologic and clinical cure was observed in 20 children, or 45 per cent of the patients, with an average of forty-nine weeks of treatment. Latent syphilis with an irreversible Wassermann reaction was observed in 18 children, or 40 per cent, but these children were practically as well as the former group. A positive Wassermann test of the blood in the absence of other clinical signs after two years' adequate treatment is not an indication for further treatment. Infection of the central nervous system, the most serious complication, occurred in 24 per cent of the children of this group, gave unsatisfactory results in 54 per cent of the children affected and demanded early and persistent treatment.

The mentality of these children was below average, and treatment had a slightly beneficial effect as judged by the estimation of the intelligence quotients, but 7 of 12 children remained below normal.

RAUH, Cincinnati. [FROM AUTHOR'S SUMMARY.]

TRYPTOPHAN BODIES IN TUBERCULOUS MENINGITIS. J. A. TOOMEY, R. P. FULTON and F. W. REA, J. Pediat. **14**:372 (March) 1939.

The tryptophan test was done on the spinal fluid in 202 cases. In this series 55 cases were proved cases of tuberculous meningitis; the remaining cases (147) were controls, in 74 of which the diagnosis was bacterial meningitis and in 73 some other meningeal condition. The results of the tryptophan test were negative in over 60 per cent of the cases of tuberculous meningitis and positive in over 23 per cent of the cases of nontuberculous meningeal irritation. The authors feel that the test is valueless as an aid to the differentiation of tuberculous meningitis from other forms of nontuberculous meningeal irritation.

RAUH, Cincinnati.

PULMONARY TUBERCULOSIS IN CHILDREN, WITH SPECIAL REFERENCE TO THE ADULT TYPES OF THE DISEASE. J. A. WILSON, Edinburgh M. J. **46**:556 (Aug.) 1939.

In a communication to the Scottish Tuberculosis Society, Wilson states that in the absence of a far reaching survey of juvenile tuberculosis in the children of

Scotland one can have recourse only to institutional figures. He discusses 386 cases in which the patients were dismissed from the Mearnskirk Hospital during the years 1934 to 1937, and he places them in six classes according to recognized clinical types of the disease.

Tuberculosis of the hilar glands was assessed in 83 children. It is an interesting type but mild and hard to prove, the sputum and gastric washing being usually free from tubercle bacilli. As a rule there is progress toward recovery, but in some cases the observations go on from simple enlarged root shadows to obvious involvement of the lungs. When the perihilar region of the lung is invaded it is possible to recover the bacilli from gastric washings; they are recovered less often from the sputum. Of 59 patients, all but 6 were dismissed in an apparently quiescent state.

Bronchopneumonic tuberculosis occurred in 19 children, all of whom were acutely ill on admission to the hospital and had tubercle bacilli in their sputum. A fatal outcome resulted in 74 per cent of these patients. A diagnosis of tuberculous pleurisy was made in 53 cases.

Miliary tuberculosis of the lungs occurred in only 8 patients. In all it was acute and fatal.

The adult type of pulmonary tuberculosis was the main concern of the author, as it appears in the children of Glasgow sufficiently often to be of serious import. There were 164 of these patients, about half the number under 10 years of age. The author discusses the distribution of the lesions, the clinical course of the disease and its complications. The most frequent complication in the respiratory system is the effusion of pleurisy, but more commonly tuberculosis invades the abdomen.

The summary indicates two features of importance: (1) the high incidence of a relatively benign type of tuberculosis in children from 6 to 10 years of age; (2) the relation of this type to the tuberculosis occurring in young adults, which is high in an industrial community and often advanced in character, owing to lack of recognition during the insidious beginning.

NEFF, Kansas City, Mo.

TUBERCULOSIS OF THE LUNGS IN CHILDHOOD: PROBLEMS AND RESULTS IN TREATMENT. C. CAMERON, Edinburgh M. J. **46**:565 (Aug.) 1939.

Cameron discusses the problems of pulmonary tuberculosis in childhood and presents the results of treatment in a sanatorium, where he gained experience as a sanatorium physician. He wishes to make the point that tuberculosis of the lungs as a clinical entity is not common in children and for that reason there is laxity in diagnosis. His experience leads him to express the opinion that children do not succumb quickly to pulmonary tuberculosis unless it is of the acute or terminal type. The primary form often heals spontaneously; the secondary form is frequently similar to the chronic disease of the adult and presents the same problems in treatment.

Enforced rest as is commonly practiced in the treatment of adults with tuberculosis is different and more difficult in the case of children. The surroundings in the sanatorium can be made interesting for the child, so that he becomes willing to rest. Quiet is also made easier by using a posterior plaster shell which fixes the child in a dorsal position. This adds to the child's comfort and in a few months helps to bring about definite improvement in cases in which by ordinary rest in bed there had been none.

Cameron discusses gold therapy and the treatment by collapse, as well as the general results from sanatorium care. When tubercle bacilli are found in the sputum, a bad prognosis is warranted. As regards the influence of age, the study shows that the child who dies of tuberculosis of the lungs in a sanatorium succumbs near puberty, the period at which the adult type begins to appear.

NEFF, Kansas City, Mo.

WHAT BECOMES OF CHILDREN SUFFERING FROM ERYTHEMA NODOSUM? F. TISSOT, Arch. de méd. d. enf. **42**:627 (Oct.) 1939.

Among patients convalescing from primary tuberculous infection who were suffering with erythema nodosum at Saint Gervais were many in whom apparently the disease did not follow the usual benign course expected. Frequent attacks of pleurisy or serious perihilar localizations occurred in children whose care had been neglected after discharge from the preventorium.

These observations confirmed those of Blechmann, published in 1937. To secure more accurate data it was decided to make a systematic study of 20 patients, the clinical histories of whom are briefly reviewed. Visceral complications were found in 9 of these children, who represented 8 per cent of the total number of children in the preventorium. A regimen was suggested, which included at least six or eight weeks rest in bed, followed by a sojourn at the sea shore or at a moderate elevation in a salubrious country district.

AMESSE, Denver.

REQUIREMENTS OF A PREVENTORIUM FOR CHILDREN FROM TWO TO FOUR YEARS OF AGE. E. LESNÉ and G. DREYFUS-SÉE, Paris méd. **1**:18 (Jan. 7) 1939.

It is emphasized that strict isolation of the patients from one another is an important factor in treating tuberculosis in the age group of 2 to 4 years. Older children are not as readily infected by each other. The other factors emphasized are cleanliness, fresh air and good food.

LESLIE, Evanston, Ill.

ARE SUBJECTS REMAINING NEGATIVE TO TUBERCULIN AFTER INJECTION OF BCG IMMUNE TO TUBERCULOSIS? J. TROISIER, M. BARIETY and P. NICO, Paris méd. **1**:22 (Jan. 7) 1939.

The consensus presented in this article is that subjects in whom a positive reaction to tuberculin does not develop after vaccination with BCG do not possess immunity and should not be returned to an environment where there is tuberculosis until revaccination has resulted in a positive reaction.

LESLIE, Evanston, Ill.

## Diseases of Blood, Heart and Blood Vessels and Spleen

CONGENITAL HEART DISEASE IN CHILDHOOD, WITH SPECIAL REFERENCE TO PROGNOSIS. R. ASH and E. HARSHAW JR., Am. Heart J. **18**:80 (July) 1939.

A review was made of the records of 230 children with congenital cardiac defects seen at the Children's Hospital, Philadelphia, during the years 1922 to 1936. Of the group of 230, 117 were boys and 113 girls. Information was obtained concerning 189 of these patients in 1938. One hundred and two children had died, and of these 73 per cent succumbed during the first year of life. The death rate of cyanotic infants was twice that of noncyanotic infants. One half of all the deaths were due to infection, pneumonia being the most frequent cause of death.

GIBSON, Chicago.

THE VALUE OF SPECIAL RADIOLOGIC PROCEDURES IN DETECTING CARDIAC ENLARGEMENT IN CHILDREN WITH RHEUMATIC HEART DISEASE. A. KUTTNER and G. REYERSBACH, Am. Heart J. **18**:213 (Aug.) 1939.

Kuttner and Reyersbach measured the "angle of clearance" (Wilson) of the left ventricle by means of a turntable in cases of mitral insufficiency, of mitral insufficiency and stenosis and of potential heart disease, as well as in normal controls. They feel that the result of such measurement is of value, especially in comparing findings in the same patient at different times.

They found that early enlargement of the left auricle could be demonstrated best by backward displacement of the barium sulfate-filled esophagus.

Measurement of the frontal area of the heart was found to be of little use in cases of early rheumatic heart disease.

GIBSON, Chicago.

INFRA-RED PHOTOGRAPHY IN HEART DISEASE. B. S. EPSTEIN, Am. Heart J. **18**:282 (Sept.) 1939.

Infra-red photographs visualized prominent and tortuous superficial veins in 3 patients with the tetralogy of Fallot. There was no evidence of congestive heart failure at the time the photographs were taken.

Control studies on normal subjects and on patients with rheumatic and hypertensive heart disease, both with and without congestive failure, did not show similar changes in the superficial veins. The present study suggests that congenital abnormalities of the superficial venous tree may be related to the cardiac malformation.

GIBSON, Chicago.

ENDOCARDITIS CAUSED BY SALMONELLA SUIPESTIFER. C. T. READ, J. Infect. Dis. **65**:263 (Nov.-Dec.) 1939.

A case of bacterial endocarditis caused by a European strain of Salmonella suipestifer is reported. American strains caused the disease in 2 cases previously reported. Read states that complete fermentation reactions must be done, with meticulous care, to identify specific members of the Salmonella group. Sulfanilamide failed to cure the endocarditis in this case. Fatal infections are produced by Salmonella suipestifer. It is the usual cause of food poisoning.

TOOMEY, Cleveland.

USE OF CLOTTED BLOOD IN TYPING AND CROSS-MATCHING BLOOD FOR TRANSFUSION. L. W. DIGGS and A. J. KEITH, South. M. J. **32**:1089 (Nov.) 1939.

A method of typing and cross-matching bloods used at the John Gaston Hospital, Memphis, Tenn., is described which utilizes paraffin rings on ordinary slides, wooden applicators and straight glass pipets, and which uses clotted blood as a source of cells and of serum.

The method is recommended because it saves time and money and is simple and safe.

SCHLUTZ, Chicago.

MONOCYTC LEUKAEMIA IN CHILDHOOD. D. COURT and D. G. EDWARD, Arch. Dis. Childhood **14**:231 (Sept.) 1939.

Two new cases of monocytic leukemia in childhood are described. The clinical features in these and in other recorded cases are analyzed and compared with those in a similar series of cases of leukemia of the lymphatic type. This analysis shows that there is no distinctive clinical picture. Certain minor differences exist, however, between the two types, notably the incidence in older persons, the longer duration, the presence of cutaneous lesions and, to a lesser degree, the distribution of the lymphadenopathy in the monocytic variety. The diagnosis is established by hematologic and histologic investigations. Examination of both blood and sternal marrow, together with a lymph gland when possible, should be carried out during life. Attention is drawn to the presence of "atypical" cells. Their occurrence in large numbers may confuse the diagnosis. It is suggested in consequence that monocytic leukemia is probably more common than is generally recognized at present.

KELLY, Milwaukee.

HYPERCHROMIC ANEMIA IN A CHILD AGED ONE YEAR. E. DOTT, Tr. Med.-Chir. Soc. Edinburgh, 1939, p. 148; in Edinburgh M. J., October 1939.

At the clinical meeting Dott showed a child who at 10 months was admitted to the hospital with lobar pneumonia, which followed the usual course to recovery

but left the child remarkably and persistently pale. At the beginning of the eleventh month the blood showed 3,000,000 red cells, 54 per cent hemoglobin and 2.6 per cent reticulocytes; a blood film showed nothing strikingly wrong, but immediate administration of iron and a suitable diet failed to build up the blood elements. Then a therapy producing a reticulocyte increase was tried, and the baby responded well. The case had been neither one of nutritional nor one of hemolytic anemia but apparently one in which there was a failure to absorb a hemopoietic factor. Such a specific response to liver therapy at an early age is interesting and rare, for pernicious anemia is not expected in young children.

NEFF, Kansas City, Mo.

ARTERIAL HYPERTENSION IN THE CHILD. R. PIERRET and G. LEFEBVRE, Arch. de méd. d. enf. **42**:545 (Sept.) 1939.

Hypertension in young subjects is rarely reported, chiefly because it is not looked for in routine examinations and, in addition, because the usual apparatus does not contain a brassard suitable for children. In the studies reported, the oscillometric method proved more accurate than the auscultatory method, although Debré prefers the latter. The dimensions of the brassard are 6 by 13 cm. A diagnosis of hypertension should be based on the findings of several successive examinations to eliminate possible variations due to accidental or transient conditions such as digestion or emotion. An increase of at least 2 cm. of mercury over the normal must be discovered before such a diagnosis may be considered, and it is consequently indispensable to adopt a rather fixed standard for age, height and weight. The formula used in the authors' examination is the following:

$$\text{Maximum} = 9 + \frac{\text{age}}{3}$$

$$\text{Minimum} = 5 + \frac{\text{age}}{5}$$

The average tension was 7.5 to 8.5.

Among the various forms of hypertension found in children, the most important is that linked with nephritis, either acute, subacute or chronic. The prognosis, however, varies with the evolution of the lesion; in the acute case the increased tension is apt to be transitory, and the outlook is good. In the hypertension of chronic nephritis, however, the status is permanent and progressive, calling for an extremely reserved opinion.

The remainder of the etiologic factors concerned with hypertension are divided into two groups, permanent and transitory. In connection with the former are mentioned the latent, primitive forms due to heredosyphilis or to dysfunction of some glandular apparatus and, in addition, the hypertension of chronic nephritis and that of congenital stricture of the isthmus of the aorta. In connection with the transitory causes mention is made of: (1) physiologic hypertension conforming to periods of growth, (2) a type associated with acute or subacute nephritis, (3) hypertension of cardiac decompensation, (4) a form due to vasomotor disturbance, (5) transient hypertension of cerebral origin as described by Samuel Amberg and (6) a rare type which may be the expression of a temporary endocrine disequilibrium.

AMESSE, Denver.

THE DIKE-VAQUEZ FOUNDATION FOR AID TO PATIENTS WITH CARDIAC DISEASE. DE JOANNIS, Rev. méd.-sociale et de protec. de l'enf. **7**:284 (July-Aug.) 1939.

The Dike-Vaquez Foundation is a private organization which was established in 1929 in Paris to provide medical and social services for patients with cardiac disease, particularly children. Careful clinical, roentgenographic and electrocardiographic studies are made and treatment provided. Rehabilitation is an important function of the foundation. Through social workers, arrangements are made for

convalescent care, and assistance is given in finding suitable living quarters. Efforts are also made to help place patients in suitable occupations when they are able to work.

BIERMAN, Washington, D. C.

ARTERIAL PRESSURE IN CHILDREN UNDER PHYSIOLOGIC AND PATHOLOGIC CONDITIONS. P. ORSINI, Med. inf., Rome **10**:301 (Oct.) 1939.

Blood pressure was determined in 119 healthy and 20 sick infants under 5 years of age. The following table shows the range of findings in the healthy children:

| | Systolic | Diastolic |
|---|---|---|
| Under 1 year | 65 to 82 | 37 to 48 |
| 1 to 2 years | 60 to 84 | 40 to 52 |
| 2 to 3 years | 70 to 82 | 42 to 48 |
| 3 to 4 years | 79 to 95 | 46 to 60 |
| 4 to 5 years | 88 to 109 | 60 to 79 |

There was essentially no difference as to sex. The ill child more often tended to have a low rather than a high blood pressure.

HIGGINS, Boston.

TUBERCULOUS POLYSEROSITIS WITH PROBABLE EVOLUTION TO CHRONIC CONSTRICTIVE PERICARDITIS. A. CASTELLANOS, B. SANCHEZ SANTIAGO and R. MONTERO, Arch. de med. inf. **8**:177 (Sept.) 1939.

A boy entered the hospital in a serious condition, with tuberculous polyserositis characterized by a double pleural flow, exudative pericarditis and an ascitic form of tuberculous peritonitis. He was given intravenous injections of calcium and of lipoids in addition to a cardiac tonic and with careful nursing made an astonishing recovery. He still has an abundant pleural secretion, and no doubt chronic constrictive pericarditis will develop.

SANFORD, Chicago.

HEREDITARY CHARACTER OF FAMILIAL ICTERUS. M. A. JAUREGUY and C. M. BARBEROUSSE, Arch. de pediat. d. Uruguay **10**:410 (July) 1939.

A hereditary factor in ichthyosis nigricans is manifest in many cases. There is no racial factor. The condition is generally observed in the male and is transmitted through the female. It can be present in successive generations, or it may skip several generations.

SCHLUTZ, Chicago.

THROMBOSIS OF THE ABDOMINAL AORTA. W. BECKER and H. GIRGENSOHN, Monatschr. f. Kinderh. **79**:180 (Aug.) 1939.

Fatal thrombosis of the abdominal aorta was observed in a 5 month old and a 16 month old child. An autopsy was performed in each case. In the first patient the infection presumably came from the intestine, working through the wall of the aorta. In the second, no etiologic factor could be found. There is a brief review of the literature.

GERSTLEY, Chicago.

A CURVE REPRESENTING THE EVOLUTION OF THE BLOOD LEUKOCYTES DURING THE FIRST YEAR OF LIFE. J. H. MAGNUSSON, Acta pædiat. **24**:63, 1939.

The curve of the total count of leukocytes during the first year of life runs parallel to the curves representing the count of red blood cells and the concentration of hemoglobin. The shape of the curve is due principally to the behavior of the polymorphonuclear cells; the lymphocytes and monocytes play only a modest role in determining its form.

MCCUNE, New York.

INVESTIGATIONS OF THE CATALASE ACTIVITY OF THE BLOOD OF CHILDREN. B. ANDERSEN, Acta pædiat. **24**:74, 1939.

The administration of iron for the cure of anemia is sometimes followed by improvement of appetite and a general tonic effect before any rise in the hemoglobin is demonstrable. This occurrence directs attention to the fact that iron is present not only in hemoglobin but in many other of the oxidative ferments of the body. The blood catalase is observed in the erythrocytes and in the white cells; it does not occur in the plasma. It can be extracted from the red cells and separated from the hemoglobin, to which it shows close chemical similarity. Catalase can be measured by its effect on the decomposition of hydrogen peroxide under controlled conditions. This technic was employed in the present investigation, the residual substrate being measured by titration with potassium iodide. Only 10 cubic millimeters of blood was required. The monomolecular velocity constant of the reaction was chosen as a measure of catalase activity; in the expression of the final result this value appears in the numerator of a fraction while the content of hemoglobin in the same specimen serves as the denominator. Specimens obtained from 85 children varying in age from 4 months to 10 years yielded catalase quotients between 17.5 and 24.2. The values for infants were somewhat lower than those for older children; premature infants showed the lowest. The comparatively small variation in the catalase quotient demonstrated clearly the close correlation between catalase activity and the hemoglobin concentration in a given specimen of blood.

McCUNE, New York.

SIMPLE MICROMETHODS FOR MEASURING THE BLOOD PHOSPHORUS AND THE PLASMA PHOSPHATASE. E. JOSEFSSON, Acta pædiat. **24**:81, 1939.

In order to reduce the size of the specimen required, Josefsson employs whole blood in place of serum for the determination of acid-soluble phosphate. The values so obtained are slightly lower than those obtained when serum is used. In conjunction with a suitable micromethod, the use of whole blood permits the estimation of phosphorus with as little as 0.15 cc. of material. Phosphatase activity is determined by using 0.1 cc. of heparinized plasma, the plasma and substrate being incubated for twenty-four hours. The amount of useful information derived from measurements of phosphatase activity in cases of rickets has been disappointingly small. Successful results are reported in the treatment of 8 patients with active rickets with massive single doses of vitamin D. [Presumably this is vitamin $D_2$.] The serum calcium and the whole blood phosphate rose promptly in all cases in which the values were low; the response of the plasma phosphatase was somewhat erratic: In general it tended to fall.

McCUNE, New York.

PLASMA PHOSPHATASE VALUES IN FINLAND. L. ARO and C. E. RÄIHÄ, Acta pædiat. **24**:91, 1939.

The average values for phosphatase in the plasma of persons of all ages is slightly higher in Helsingfors, Finland, than in Denmark. Does this indicate a generalized deficiency in vitamin D on the part of the Finnish population?

McCUNE, New York.

THE ELECTROCARDIOGRAM OF CONGENITAL HEART DEFECTS. E. MANNHEIMER, Acta pædiat. **24**:128, 1939.

In 20 cases of congenital heart disease with marked cyanosis the electrocardiographic records revealed pathologic features. In most of the cases there was marked right-sided preponderance, and in many, enlarged auricular and ventricular complexes. In several instances the PR interval was prolonged and the ST interval shortened. In a group of 54 cases of congenital cardiac defect with-

out cyanosis the electrocardiograms were normal in only one third. The other two thirds of the group showed abnormalities in the form of the ventricular complexes. Left-sided preponderance occurred somewhat more frequently than right-sided preponderance.

McCUNE, New York.

THE EVOLUTION OF THE NUMBER OF LEUKOCYTES DURING THE FIRST YEAR OF LIFE: A COMPARISON BETWEEN FULL TERM INFANTS AND PREMATURE INFANTS. J. H. MAGNUSSON, Acta pædiat. **23**:259, 1939.

The present study concerns itself with the curve of development of the number of blood leukocytes in a series of 52 premature infants who weighed 2,250 Gm. or less and were 3 weeks to 1 year of age. The author compares the results obtained in this series with those of a similar investigation carried out with 47 full term infants of comparable ages, weighing between 3,000 and 3,500 Gm. The leukocyte count of the premature infants was consistently lower than that of infants born at term. At a given age the premature infants had a lower total white count, as well as lower percentages of granular elements, lymphocytes and mononuclear cells. Large fluctuations with respect to all variables were observed in both series.

McCUNE, New York.

POLYCYTHAEMIA VERA AND TOWER SKULL IN A CHILD. O. H. DYKSTRA and T. HALBERTSMA, Maandschr. v. kindergeneesk. **9**:12 (Oct.) 1939.

At autopsy on a child with polycythaemia vera and oxycephaly (compare Halbertsma, T.: Polycythemia in Childhood with Report of a Case in a Boy, Six Years Old, with Tower Head, AM. J. DIS. CHILD. **46**:1356 [Dec.] 1933) who died after seven years' observation, at the age of 12 years, of septicemia, a severe degree of thickening of the skull cap was found. Of this change nothing could be seen in the roentgenogram taken six years earlier. The same change is found in the erythroblastic anemia of Cooley, in sickle cell anemia and sometimes in hemolytic anemia. The observations of the authors prove that, together with these three diseases, there exists a fourth blood disease of which this is a symptom.

VAN CREVELD, Amsterdam, Netherlands.

A CASE OF ACUTE HEMOLYTIC ANEMIA (TYPE LEDERER) AFTER SCARLATINA. H. BEEKMAN, Maandschr. v. kindergeneesk. **9**:34 (Oct.) 1939.

A boy of 2 years had scarlatina, with a normal course. Later acute hemolytic anemia (type Lederer) developed. Blood transfusions were given and were followed by a quick recovery. The observation is reported as supporting the allergic origin of this syndrome occurring after an infection (in this case, streptococcic) in a predisposed person.

VAN CREVELD, Amsterdam, Netherlands.

## Diseases of Nose, Throat and Ear

CHRONIC OTITIS MEDIA IN CHILDREN AS A GENERAL DISEASE WITH SPECIAL REFERENCE TO VITAMIN C METABOLISM. K. BERNFELD, M. FEILCHENFELD and W. HIRSCH, Ann. pædiat. **153**:222 (July) 1939.

Local treatment of chronic otitis media in children has not given favorable results. Prophylactic measures play a more important role. With a view to controlling the general factors influencing inflammations of the middle ear, 53 children from 6 months up to 10 years of age have been taken under clinical observation. A test for hypovitaminosis C was made by the saturation method in every child. Fifty per cent of these children were of decreased resistance and in poor nutritional condition. The values for hemoglobin were slightly decreased; the blood picture was normal. More than 30 per cent of the children showed tonsillar foci of infection and adenoid vegetations. In the majority suppurative otitis had

lasted for one to three years. In more than 50 per cent of these patients with chronic otitis with the same nutrition a marked deficit in the output of vitamin C was found. The hypovitaminosis occurred in a higher percentage of the group of poorly nourished, slightly anemic children with decreased resistance than of the children in good condition. No relation could be detected between duration of illness and hypovitaminosis.

A series of children living under the same conditions but suffering from acute otitis were nearly all found to have a normal output of vitamin C. The hypovitaminosis C which is found in children with chronic otitis in contrast to those with acute otitis seems to relate to some constitutional factor.

FROM AUTHORS' SUMMARY.

HEMORRHAGES AFTER TONSILLECTOMY. E. G. OSER, Monatschr. f. Ohrenh. **73**:112 (Feb.) 1939.

Oser has observed among 12,241 tonsillectomies, 93 postoperative hemorrhages (0.75 per cent). Of 3,121 operations performed with the patient under local analgesia, 65 were followed by hemorrhages (2 per cent) and of 9,120 operations with the patient under general anesthesia, 28 were followed by hemorrhages (0.3 per cent). Among 7,303 adenoidectomies he has observed but 3 postoperative hemorrhages. From these figures it follows that the danger of postoperative hemorrhages in general is greater in tonsillectomies performed under local analgesia than in those performed under general anesthesia. The author further states that this danger is generally greater among adults than among children and that, as far as the adenoidectomies are concerned, this danger is diminished to a great extent if, after the operation, the epipharynx is examined by palpation for remains of adenoid tissue.

LEDERER, Chicago. [ARCH. OTOLARYNG.]

SYMPTOMS AND COURSE OF MASTOIDITIS FOLLOWING OTITIS FROM SWIMMING. M. BUCHBAND, Monatschr. f. Ohrenh. **73**:332 (May) 1939.

A special type of surgical otitis, produced by infections acquired in swimming, is evaluated by the author. The infection can occur by way of the eustachian tube or by way of a rupture of the drum occurring, for example, in diving or in water polo. In seven years 20 such cases of surgical otitis were observed at the Neumann otologic clinic. In 16 of these the former and in 4 the latter path of infection was noted. All varieties of bacilli were found with this type of otitis, but the author cites an epidemic of 21 infections with the Friedländer bacillus. The course in all the cases in no way differed from that of other forms of surgical otitis, except that the death rate was double the normal, ruptured drums especially producing a more fulminant course. It may be reasoned that in these cases the infection meets no adequate resistance by the mucous membrane, because of its rapid onset.

LEDERER, Chicago. [ARCH. OTOLARYNG.]

ABSCESS OF THE PARAPHARYNGEAL LYMPH GLANDS FOLLOWING INFECTIONS OF THE THROAT. R. WALDAPFEL, Pract. oto-rhino-laryng. **2**:69 (April) 1939.

Waldapfel groups the complications of infections of the throat into (1) the hematogenous form, in which an infection from the tonsils and the thrombosed tonsillar veins may pass directly into the blood stream without involvement of the cervical or pharyngeal glands and without formation of an abscess; (2) the lymphogenous form, in which infection of the blood stream may come from the regional infected glands or abscess, causing periphlebitis or thrombophlebitis of the larger veins, and (3) the interstitial or phlegmonous form, in which there is an invasion of the parapharyngeal spaces, either toward the mediastinum or cephalad, with or without involvement of the veins, and either proximal or distal to the primary focus of infection. It is the third group that he emphasizes in his discussion, i. e., the group in which frank abscesses occur in the pharyngeal spaces.

He presents a group of patients in whom inflammatory swelling in the neck has followed infection of the throat. While this infection may be recent and rather severe, it is not always so, since some of his patients complained of only the mildest and most transient symptoms referable to the throat. The swelling in the neck varies from the size of a plum to that of a small apple. It is usually rather hard, somewhat painful to the touch and generally adherent, and the overlying skin is not freely movable. However, fluctuation is not always present. The tonsils invariably appear rather innocent, in that they do not show either an acute process or any evidence of the origin of the infection. The pharynx is usually asymmetric because of the swelling of the lateral oropharynx or hypopharynx. In Waldapfel's patients the temperature was not particularly significant, ranging from subnormal to only slightly elevated. However, when he observed a decided sudden rise of temperature, he always suspected a general spread of the infection. The local symptoms are usually only slight in the early stages. Frequently pain is referred to an ear, and then, with increase in swelling, there is some difficulty in swallowing and some limitation of motion of the head. Pathologically, there is evidence of an abscess of the cervical lymph glands which extends and spreads into the parapharyngeal spaces. The course of this abscess varies. First, complete resolution, with resorption of the exudate and complete return of the gland to normal size and function, may occur. Second, contact infection of the veins in the vicinity may develop, with subsequent thrombophlebitis and septicemia. This usually is due to a spread of the infection, arising from the glands that surround the regional veins and thus, by contiguity, causing the thrombophlebitis. In cases in which this had occurred, evidence of encapsulation of the diseased process was not usually observed. Finally, the third course is breaking down of the glands and formation of an abscess. This is a slow progressive course, the glands usually becoming confluent; a rather dense capsule is formed, and the abscess slowly spreads both externally toward the skin and internally into the parapharyngeal spaces. Because of the slower course and the accompanying inflammation, adhesions and pocketing of the subcutaneous tissues are frequent. The cause of the differentiation into the three pathologic groups is uncertain, but the author suggests that the differentiation may depend on either the virulence of the organism or the resistance of the patient. He differentiates cervical adenopathy from actinomycosis, glandular involvement in leukemia and other dyscrasias of the blood, malignant adenitis (which may be metastatic from another source) and chronic cervical lymphomas.

The treatment in the first stage is expectant, i. e., application of antiphlogistics—heat, infra-red rays and short waves. The abscess rarely ruptures spontaneously unless there is an extensive underlying disease or complication. However, should the infection continue into the second stage, with progression of symptoms, such as laryngeal edema, a sudden rise in temperature, chills or marked spread of the infection to the vertebrolaryngeal spaces, as seen by roentgen examination, surgical intervention is necessary. The external approach should be used. The postoperative course is usually uneventful, unless the patient has generalized septicemia, which must then be treated per se.

In conclusion, the author states that the connective tissue of the skin has two main roles. First, it can favor the spread of a suppurative process in either an upward or a downward direction, and, second, it is capable of encapsulating this process and so limiting its progress. It is in this manner that it plays an important role in complications of any infection of the throat.

PERSKY, Philadelphia. [ARCH. OTOLARYNG.]

ROENTGEN TREATMENT OF ACUTE OTITIS MEDIA. P. MENCK-THYGESEN, Pract. oto-rhino-laryng. **2**:105 (April) 1939.

The author reports the results of roentgen therapy in the treatment of a series of 110 patients with acute otitis media. One hundred and seventy-two ears were involved.

His technic varied with the age of the patient. For those up to 2 years he used 100 roentgens with a filter of 4 mm. of aluminum; for those from 2 to 8 years, 150 r with a filter of 4 mm. of aluminum; for those from 8 years to early adult life, 200 r with a filter of 4 mm. of aluminum, and for adults, 200 r with a filter of 0.5 mm. of copper and 2 mm. of aluminum. Sixty-two of his patients required only one treatment; for 47 the treatment was repeated within eight days, and only 1 patient required three exposures. Paracentesis was done in all the cases, whenever indicated. In addition, the usual local treatment was instituted to maintain drainage and cleanliness.

The author made a comparison of a number of cases of patients treated with the ordinary routine and his group of patients treated by roentgen rays, and found that in the latter group 20 per cent of the patients were less likely to require operative intervention. In addition, the duration of the discharge was markedly decreased: The average length of discharge was eleven and three-tenths days. However, the latter fact was influenced by the time of institution of treatment, for the author found that when treatment was started early after the onset of the infection, particularly in what he terms the presuppurative stage, the results were decidedly better. Untoward effects did not follow the treatment, and he disputes the development of such complications as falling of the hair, dermatitis or disturbance of hearing. In his series, 23 patients did not improve with treatment and had to be operated on.

In summarizing, he states that the treatment is painless, that the operative percentage is definitely lowered and that the duration of the discharge is shortened. The contraindications are fulminant progressive mastoiditis, extensive bony destruction of the mastoid cells as seen on roentgen examination and the onset of any intracranial complications. PERSKY, Philadelphia. [ARCH. OTOLARYNG.]

A SOLITARY OSTEOMA OF THE ETHMOID LABYRINTH EXTENDING INTO THE ORBIT. W. SCHOLZ, Ztschr. f. Hals-, Nasen- u. Ohrenh. **45**:86 (March) 1939.

An osteoma of the ethmoid labyrinth which extended into the orbit in a 16 year old patient is reported. The patient had not complained of any previous symptoms referable to the nose or throat, but had noticed that for the past two to three years the eyes were slowly distorted outward and forward. Pain, disturbance of vision or interference with breathing did not occur.

Examination revealed a hard crescentic swelling on the nasal wall of the orbit. Roentgen examination revealed a massive shadow extending into the right orbit, irregular in outline but sharply defined, with a pedicle extending into the right ethmoid labyrinth.

At operation the author found a hard white tumor, which was freely outlined and was attached to the ethmoid labyrinth by a short pedicle. He was able to remove the wall of the labyrinth without laceration of its mucous membrane. The patient recovered without any untoward events.

Histologic examination showed the tumor to be a fibro-osteoma.

PERSKY, Philadelphia. [ARCH. OTOLARYNG.]

## Diseases of Lungs, Pleura and Mediastinum

OBSERVATIONS ON THE EXPERIMENTAL AND CLINICAL USE OF SULFAPYRIDINE: III. THE MECHANISM OF RECOVERY FROM PNEUMOCOCCAL PNEUMONIA IN PATIENTS TREATED WITH SULFAPYRIDINE. W. BARRY WOOD and PERRIN H. LONG, Ann. Int. Med. **13**:612 (Oct.) 1939.

Sulfapyridine acts as a bacteriostatic agent in pneumococcic infections. Recovery from pneumococcic pneumonia is dependent on phagocytosis. Type-specific antibodies do not appear in the blood until several days after the temperature has reached normal. Administration of sulfapyridine should be continued until antibody formation has occurred. READING, Galveston, Texas.

SULFAPYRIDINE THERAPY IN THE PNEUMONIAS OF INFANCY AND CHILDHOOD. JEROME S. LEOPOLD and IRWIN PHILIP SOBEL, Arch. Pediat. **56**:581 (Sept.) 1939.

Fifty-eight infants and children with lobar pneumonia and bronchopneumonia were treated with sulfapyridine. One fatality occurred.

Jaundice from toxic hepatitis occurred in 2 patients.

The temperature fell to normal in 54 of the 58 cases within forty-eight hours after administration of the drug had been started. In 49 cases favorable response occurred within thirty-six hours, and in 35 cases, within twenty-four hours.

In 22 cases sulfapyridine therapy was started two days or less after the onset of the disease. In 16 of these the duration of the illness was three days or less.

Compared with specific antipneumococcus serum, sulfapyridine has a particular advantage in the treatment of the pneumonias of infancy and childhood. It may be administered as soon as the diagnosis is made, thus avoiding the one day's delay until pneumococci can be cultured from the pharyngeal material and typed.

ORR, Buffalo.

THE TREATMENT OF PNEUMONIA IN INFANTS AND CHILDREN WITH SULFAPYRIDINE. CHARLES J. BAKER and HARRY NAUMER, Brooklyn Hosp. J. **1**:217 (Oct.) 1939.

This report concerns patients with pneumonia in the pediatric department of the Brooklyn Hospital from Feb. 1 to June 1, 1939, who were treated with sulfapyridine. Fifty-three patients were so treated, without serum therapy. The pneumonia was due to a variety of organisms. The only complication was acute otitis media, which occurred in 22.6 per cent of the cases. Toxic manifestations were slight. Recovery in three days took place in all but 1 of the children. This patient had bronchopneumonia caused by Pfeiffer's bacillus and complicating a congenital cardiac lesion which had been associated with cyanosis before the onset of the pneumonia.

LESLIE, Evanston, Ill.

PRELIMINARY REPORT OF THE USE OF SULFAPYRIDINE IN THE TREATMENT OF PNEUMONIA. NORMAN PLUMMER and HERBERT ENSWORTH, Bull. New York Acad. Med. **15**:241 (April) 1939.

This is a preliminary report on a study of 111 cases of pneumonia over a period of three months. Typical and atypical acute pneumonias are included without special reference to the organism responsible for the condition. As to the disadvantages of the drug, 55 per cent of the patients had nausea, and 40 per cent had both nausea and vomiting. In 10 per cent of cases sulfapyridine had to be discontinued because of the severity of the gastrointestinal symptoms.

Eighty-eight patients had definite signs of pneumonia. Of these, 28 received specific antipneumococcus serum in addition to the sulfapyridine.

The author concludes cautiously that there is some evidence even from this small series of cases that a combination of sulfapyridine with serum gives greater benefit than does either of these agents alone.

JAHR, Omaha.

PRELIMINARY REPORT ON THE USE OF SULFAPYRIDINE IN THE TREATMENT OF PNEUMONIA. HARRISON FITZGERALD FLIPPIN, Bull. New York Acad. Med. **15**:249 (April) 1939.

This paper is part of a symposium on the treatment of pneumonia with sulfapyridine, delivered before the Academy of Medicine of New York. This report is based on a series of 100 cases in which pneumonia was treated with the drug. The mortality was 8 per cent, as compared with 27 per cent in the control series.

JAHR, Omaha.

PNEUMOCOCCUS TYPE XIV PNEUMONIA IN TWINS; CONTRASTED TREATMENT. JESSE G. M. BULLOWA, J. A. M. A. **112**:1247 (April) 1939.

Seventeen month old twins had a "pulmonary and blood stream infection" with pneumococcus type XIV after measles. Prompt treatment of one with serum gave an early cure. The other, after a stormy course, recovered promptly when late treatment with serum was given. HEERSMA, Kalamazoo, Mich.

THE ROLE OF ALLERGY IN BRONCHIECTASIS. SAMUEL H. WATSON and CHARLES S. KIBLER, J. Allergy **10**:364 (May) 1939.

A study of 46 cases of bronchiectasis in the clinic of the authors at Tucson, Arizona, revealed that a high percentage of patients had definite evidence of allergy based on the presence of hay fever, asthma, nasal polyps, atopic dermatitis and abnormal amounts of eosinophils in the nasal or bronchial secretions, excluding cutaneous tests entirely. They feel that bronchiectasis can be closely simulated by basal allergic bronchitis, that bronchitis can be favorably influenced by allergic management and that the association of sinusitis and bronchiectasis can be explained on a basis of allergy. HOYER, Cincinnati.

MEDIASTINAL TUMORS IN CHILDREN: REPORT OF CASE. D. B. MONSKY, J. M. A. Alabama **9**:37 (Aug.) 1939.

The author reports a case of mediastinal tumor in an infant 14 months of age (roentgen diagnosis). There was an initial paucity of intrathoracic symptoms, the primary difficulty noted by the parents being edema of the child's legs, feet and eyelids. Approximately one month after the occurrence of these symptoms rapid breathing and cyanosis developed, followed by death. Autopsy was not permitted. WEIGAND, Indianapolis.

THE USE OF SULFAPYRIDINE IN PRIMARY PNEUMOCOCCIC PNEUMONIA AND IN PNEUMOCOCCIC PNEUMONIA ASSOCIATED WITH MEASLES. HORACE L. HODES, WILLIAM C. STIFLER JR., ETHEL WALKER, MACLYN MCCARTY and ROBERT G. SHIRLEY, J. Pediat. **14**:417 (April) 1939.

Seventy-one children ranging in age from 4 months to 9 years with pneumonia proved by roentgen examination were treated with sulfapyridine. Thirty-three children had primary pneumonia, and in 38 pneumonia was associated with measles. Typable pneumococci were isolated from the nasopharynx in each instance. Types 14 and 1 predominated. Type 14 was obtained twelve times from children under 2 years of age and twice from patients over that age. Type 1 was obtained once from a child under the age of 2 years and 8 times from children over that age. Sulfapyridine was administered by mouth. The dose varied between 1.2 and 6.0 Gm. in twenty-four hours, depending on the age of the child. The drug was given every six hours, and in many instances the twenty-four hour dose was given at once, on admission. In most cases the drug was continued until the temperature had been normal from five to eight days. It was continued for a longer period when otitis media or infected fluid was present. All the patients recovered. In nearly every case the temperature became normal, and definite improvement took place within forty-eight hours after institution of treatment. Granulocytopenia in a mild form occurred 5 times and in a more severe form once. Gross hematuria was seen in 2 patients. Another patient who received the sodium salt of sulfapyridine intravenously in addition to the drug by mouth also developed hematuria. Addis counts and tests of renal function revealed no permanent renal damage. One child had a morbilliform rash, fever and vomiting. These symptoms disappeared within eight hours after withdrawal of the drug. RAUH, Cincinnati.

THE TREATMENT OF PNEUMONIA WITH SULFAPYRIDINE. JACK BASMAN and W. L. COOKE, West Virginia M. J. **35**:209 (May) 1939.

The authors report the cases of 31 hospitalized patients with pneumonia, in which sulfapyridine was used. The only death in 17 cases of lobar pneumonia occurred six hours after admission. Fourteen cases of bronchial pneumonia are included, with 1 death. There was no mortality among the 11 infants and children in the series. Toxic reactions were not marked, but 1 patient had a rash, and another had leukopenia (leukocyte count, 3,400 per cubic millimeter) without clinical signs of agranulocytic angina. The dosage was based on body weight with no allowance for age; 0.05 Gm. of sulfapyridine per kilogram of body weight was given as an initial dose and followed by a similar amount each twenty-four hours in six divided doses. No conclusions were made regarding the optimum concentration of sulfapyridine in the blood. FROM THE AUTHORS' SUMMARY.

TRANSIENT PULMONARY INFILTRATION WITH BLOOD-EOSINOPHILIA (LOEFFLER'S SYNDROME). F. PARKES WEBER, Brit. J. Child. Dis. **36**:15 (Jan.-March) 1939.

The author cites the case of a 10 year old boy in whom a roentgenogram of the chest showed an opacity of the lobe of the right lower lung which two weeks later had disappeared. The history of the illness and clinical course are fragmentary. For the latter half of his illness he was observed in the hospital, where the disease ran an afebrile course. The Moro tuberculin reaction was negative. The blood picture was normal except for moderate eosinophilia (eosinophils 7 to 13 per cent). No intestinal parasites were found.

The author surmises that this may be an instance of Loeffler's syndrome.

LANGMANN, New York.

TREATMENT OF EMPYEMA BY HIGH NEGATIVE PRESSURE DRAINAGE. E. R. TRETHEWIE, Brit. J. Surg. **27**:58 (July) 1939.

The author reviews briefly the literature on empyema and points out the unsatisfactory results obtained at present. He outlines a technic for closed drainage. A strong negative pressure is induced. This negative pressure is at first placed at 40 mm. of water and is increased daily by 2.5 cm. until a pressure of 22.5 cm. of mercury is obtained. Early rib resection is advocated, with closed drainage and negative pressure as soon as the empyema is diagnosed. If the child is too ill for rib resection, insertion of the drainage tube with the region under local anesthesia is undertaken instead. Eighteen cases of empyema in children treated by this method are reported in summary. All the children recovered.

KEITH, Toronto, Ontario.

## Diseases of the Gastrointestinal Tract, Liver and Peritoneum

CONGENITAL TRACHEOESOPHAGEAL FISTULA WITHOUT ATRESIA OF THE ESOPHAGUS: REPORT OF A CASE WITH PLASTIC CLOSURE AND CURE. C. J. IMPERATORI, Arch. Otolaryng. **30**:352 (Sept.) 1939.

The successful treatment of a congenital tracheoesophageal fistula is reported. Embryologic and etiologic considerations and the incidence of anomalies of this type are presented, and particular attention is called to the operative procedure and to the conflicting symptoms which complicated diagnosis.

GREENWOOD, Chicago.

STRANGULATED INGUINAL HERNIA IN INFANTS. R. B. EATON, Canda. M. A. J. **42**:66 (Jan.) 1940.

Although inguinal hernia is probably one of the commonest congenital anomalies in infants, the complication of strangulation is considered to be rare. Only few

cases have been reported. Eaton reports the condition in a 4 week old baby. Operation disclosed strangulation of a loop of small intestine at the inner ring of an inguinal hernial sac. Complete recovery followed the operation.

MOORE, Omaha.

TREATMENT OF IRREDUCIBLE INTUSSUSCEPTION DUE TO MECKEL'S DIVERTICULUM. R. STUPPEL, Brit. M. J. **2**:722 (Oct. 7) 1939.

Stuppel reports a case as outlined in the title of the paper. There is sounded a special caution relative to Meckel's diverticulum and an admonition as to complete excision of the tumor and diverticulum.

ROYSTER, University, Va.

STEATORRHEA. L. HUGHES, M. J. Australia **2**:671 (Nov. 4) 1939.

Confining his remarks chiefly to celiac diseases, Hughes presents a fine discussion of the various aspects of the general subject of steatorrhea. He is inclined to agree with Thaysen that celiac disease, nontropical sprue and tropical sprue should be considered as one disease and grouped under one designation, "idiopathic steatorrhea."

GONCE JR., Madison, Wis.

FAMILIAL HEPATITIS. F. B. PARSONS, Proc. Roy. Soc. Med. **32**:1197 (Aug.) 1939.

Parsons describes a family affected with familial hepatitis. There were 9 children in the family; 2 were alive and well; 2 were alive but had hepatic enlargement; 4 had died from hepatic failure, and 1 child had died probably of some other cause. No member of the family had suffered from icterus neonatorum, and in no case had there been any suggestion of retardation of growth. Both parents were alive and well; they had not suffered from relevant illnesses in the past, and so far as can be ascertained there had been no hepatic dysfunction on either side. The histories of the patients are given in detail, including the autopsy reports on the 2 patients who died from hepatic failure.

WILLIAMSON, New Orleans.

PLASMA PHOSPHATASE IN JAUNDICE IN CHILDREN. W. W. PAYNE, Proc. Roy. Soc. Med. **32**:1265 (Aug.) 1939.

Payne investigated 54 cases of jaundice. Of these, 31 were cases of catarrhal jaundice, epidemic in type, closely resembling the epidemic type described by Lisney. The remaining cases were: 1 case of obstructive jaundice due to stone; 8 cases in which two or more attacks of jaundice occurred, and 14 cases in which the jaundice could not be classified. In several of the latter it followed an acute febrile illness, such as bronchitis or influenza (in an epidemic). In 5 cases it had the symptomless onset of infective hepatitis, and 2 of the patients were in contact at home with persons who had jaundice.

The general conclusion is that plasma phosphatase is high in the early stages of catarrhal jaundice but rapidly falls, whereas in infective hepatitis it tends to be higher and the elevation lasts longer. At any rate, estimations of the plasma phosphatase in children should be helpful in detecting mild infective hepatitis, and the subjects should not be regarded as cured if the phosphatase has not returned to normal. It is not possible to make a clearcut distinction between the two types of infective jaundice clinically or epidemiologically, and it is quite possible that they are variants of the same disease.

The paper is accompanied by a case report and tables showing the relation between the onset of jaundice and the level of plasma phosphatase in the two types of jaundice.

WILLIAMSON, New Orleans.

ANESTHETIZATION OF DORSAL NERVE FOR MEGACOLON. V. CLIMESCA, P. SARBU, and S. ROMAN, Presse méd. **47**:1118 (July 15) 1939.

A case of megacolon is presented in a boy of 12. Following Hibbs's method, 100 mg. of procaine hydrochloride was used to anesthetize the dorsal roots. A second treatment, with 70 mg. of the drug, produced a complete cure. This seems to indicate the presence of hypersympathicotonus, which is overcome by the anesthesia. The parasympathetic system then reestablishes intestinal motility.

DAFFINEE, Boston.

CONGENITAL MALFORMATIONS OF THE RECTOANAL REGION. O. MARGARUCCI, Med. inf., Rome **10**:257 (Sept.) 1939.

Three types of congenital atresia of the rectum and anus are to be found: (1) atresia limited to the anus only, (2) atresia involving the rectum, with or without a normal anus, and (3) absolute failure of formation of either rectum or anus.

A frequent accompaniment of atresia of the rectum is a fecal fistula to the vagina, bladder or ureter.

HIGGINS, Boston.

GLYCOGEN OF THE LIVER IN EXPERIMENTAL KETOSIS. P. SCHIAPARELLI and A. DORDI, Riv. di clin. pediat. **37**:961 (Dec.) 1939.

Ketosis may be produced in rats and rabbits by a diet of lard and cheese; if olive oil is also given parenterally, the ketosis appears sooner and to a greater degree. Destruction of hepatic glycogen increases proportionally to the increase in ketosis and is probably an important factor in the genesis of the ketone acids.

HIGGINS, Boston.

FOREIGN BODIES IN THE DIGESTIVE AND RESPIRATORY TRACTS IN CHILDREN. A. CODINACH Y SEGURA and R. PERCEIRAS, Arch. de med. inf. **8**:210 (Sept.) 1939.

Eleven cases of foreign body in the digestive or the respiratory tract of a child are presented. The foreign body most frequently observed in the esophagus was the metal toy jack; one was expelled orally and two rectally. Vegetable foreign matter in the respiratory tract is of the greatest danger to a child under 2 years of age. Bronchopneumonia and atelectasis are the common complications. Children under 4 years of age do not take a general anesthetic well; immediate extraction is necessary and careful nursing afterward. The mortality in this series of cases was between 3 and 4 per cent.

SANFORD, Chicago.

ACUTE INTUSSUSCEPTION IN NURSLINGS; REDUCTION BY BARIUM SULFATE ENEMA. L. A. PIERONI, Arch. de pediat. d. Uruguay **10**:299 (May) 1939.

In 6 cases of acute intestinal intussusception in nurslings Pieroni employed the barium sulfate enema. In all of them he obtained complete reduction. Early recognition of the intussusception and use of the barium sulfate enema within the first twenty-four hours are important factors in successful use of this treatment. The reduction can be followed by roentgen examination. If the invagination is successfully reduced, the alarming symptoms disappear promptly and are followed by tranquil sleep.

SCHLUTZ, Chicago.

BILIRUBINEMIA IN JAUNDICE OF THE NEWBORN. V. FUENTES, R. CANZANI and A. GRANA, Arch. de pediat. d. Uruguay **10**:389 (July) 1939.

A physiologic hyperbilirubinemia was observed in jaundice of the newborn. The average value was 1.06 mg. of indirect bilirubin per hundred cubic centimeters of blood. This is three and a half times higher than the average adult value.

During the first few days of life the hyperbilirubinemia falls rapidly until the fourth day. During the first month there is notable hypobilirubinemia. Physiologic icterus occurs exclusively at the expense of indirect bilirubinemia. The highest value of bilirubinemia observed in any case was 12 mg. per hundred cubic centimeters. There are very marked differences in the bilirubinemia curves in pathologic jaundice of the newborn. An enormous increase of indirect bilirubin was observed in a case of icterus gravis neonatorum. SCHLUTZ, Chicago.

ULCERS OF THE GASTROINTESTINAL TRACT IN CHILDREN. E. WEGENER, Monatschr. f. Kinderh. **79**:147 (Aug.) 1939.

Wegener reports a case of duodenal ulcer in infancy, with the observations at autopsy, and reviews the literature. Ulcers of the gastrointestinal tract occur in the period from the first to the fifth year more commonly than is generally supposed. Because the symptoms are few or indefinite, the lesion is rarely diagnosed except when it is in the most advanced stage. Wegener attempts to relate the duodenal ulcer which he observed in an infant to measles bronchopneumonia and gastrointestinal allergy. His discussion is highly speculative. GERSTLEY, Chicago.

ACETONE VOMITING. W. GOETERS, Monatschr. f. Kinderh. **79**:176 (Aug.) 1939.

This is a report of acetone vomiting in a 3 year old child, ending fatally. Autopsy disclosed only fatty infiltration of the liver and of the cortex of the adrenal. GERSTLEY, Chicago.

ELECTROCARDIOGRAPHIC INVESTIGATIONS IN PYLOROSPASM. E. LIMPER, Monatschr. f. Kinderh. **79**:202 (Aug.) 1939.

Limper reports cases and gives curves showing the effects of pylorospasm on the electrocardiogram. In 70 per cent of the cases the electrocardiogram showed a prolongation of systole. At the same time, changes in the T wave occurred. The hypothesis is offered that these findings are the result of a diminution in the supply of oxygen to the heart following coronary spasm.

GERSTLEY, Chicago.

DISTURBANCES IN SUCKING. A. PEIPER, Monatschr. f. Kinderh. **79**:241 (Aug.) 1939.

Peiper submits tracings attempting to show that the rhythm of the sucking center may suppress the rhythm of the respiratory center. In the sick infant there is frequently a disturbance of this control, so that the influence of the sucking center on respiration is not so constant. The writer pictures three different steps in the creation of an abnormal interrelationship, the first being a marked inhibition of respiration by the sucking center; in the third stage the centers conduct independent rhythms.

The interdependence of the two centers can be demonstrated during the first meal of the newborn. GERSTLEY, Chicago.

THE ROENTGEN FEATURES OF CHRONIC CECOCOLIC INTUSSUSCEPTION. E. J. KNOFLIČEK, Röntgenpraxis **11**:284 (May) 1939.

A 6 year old girl had suffered from recurrent attacks of abdominal pain for almost a month. Physical examination and a barium sulfate enema revealed intussusception. In view of the long duration of the illness, a test meal with an opaque substance was thought to be permissible. Roentgen films obtained six hours after the ingestion of the contrast medium showed the head of the column of barium sulfate to have reached the sigmoid; the ileum was visualized as a contracted band that extended through the ascending and transverse colon, where it had been pulled as the head of the intussusceptum progressed caudally; the head

of the intussusception was clearly visualized in the middle of the descending colon. Operation demonstrated that the mishap was due to exaggerated mobility of the cecum and ascending colon, as is usually the case in this type of intussusception. Complete reduction was not possible; partial resection with side to end anastomosis was followed by uneventful convalescence.

McCUNE, New York.

DISEASE OF THE MESENTERIC GLANDS IN CHILDHOOD. E. PLAAS, Deutsche Ztschr. f. Chir. **251**:582 (Feb.) 1939.

Mesenteric lymphadenopathy, found at laparotomy, was caused by appendicitis in 12 cases, by enteral infections in 10 cases, by parenteral infections in 5 cases, by tuberculosis in 5 cases and by neurogenic bowel dysfunction in 9 cases. The high fever, poorly localized epigastric pains and general abdominal tenderness seen occasionally in appendicitis may be due to the accompanying adenitis, since these symptoms are also found in adenitis secondary to acute enteral and parenteral infections. In the latter group, a general intestinal catarrh may be responsible. Peritonitis due to rupture of a lymph gland after dysentery is reported. Tuberculous adenitis is comparatively rare. Nonspecific adenitis was found in 9 children who complained of recurrent diffuse abdominal pains, anorexia, nausea, vomiting, bowel irregularity and failure to gain weight. One patient had irregular spasms and dilatations of the bowel, pointing to sympathetic disturbances which may have been caused by the tuberculous destruction of the ten to twelve thoracic vertebrae which was found one and one-half years later on roentgen examination.

HARRIS, Durham, N. C.

SURGICAL TREATMENT OF HYPERTROPHIC PYLORIC STENOSIS IN BABIES. R. DYKHUIZEN, Nederl. tijdschr. v. geneesk. **83**:5053 (Oct. 21) 1939.

The results of surgical treatment of hypertrophic pyloric stenosis in 130 infants in the surgical clinic of Groningen, Netherlands, are reported. Seven of the babies died. In not a single case was operation refrained from in view of the poor general condition. The prognosis of an accidental lesion of the mucosa occurring in the act of cleavage of the muscular coat is good if only the lesion is found in time and treated. Stress is laid on the importance of removing the last obstructing muscle fibers on the duodenal side. The results of the follow-up study of the infants operated on were favorable.

VAN CREVELD, Amsterdam, Netherlands.

## Nervous Diseases

AGE OF ONSET OF EPILEPSY: DIFFERENCE BETWEEN DETERIORATED AND NON-DETERIORATED PATIENTS. H. A. PASKIND and M. BROWN, Am. J. Psychiat. **96**:59 (July) 1939.

Writers on epilepsy are mostly workers in institutions and colonies for epileptic patients. Most of the data pertaining to the age of onset of epilepsy therefore concern patients with severe epilepsy and not infrequently those of the deteriorated type. This report is based on a study of 368 adult nondeteriorated patients with epilepsy from the private practice of Dr. Hugh T. Patrick and from the outpatient clinic of Northwestern University Medical School. None of the patients included here had suffered from the syndrome less than six years. The data thus obtained were compared with those prevailing for institutional deteriorated patients. The conclusions drawn are as follows:

Fewer nondeteriorated patients have the onset before the age of 5 years.
Fewer nondeteriorated patients have the onset before 10 years of age.
More nondeteriorated patients have the onset after 20 years of age.
More nondeteriorated patients have the onset after 40 years of age.

JAHR, Omaha.

FREQUENCY OF SEIZURES IN EPILEPSY: DIFFERENCES BETWEEN DETERIORATED AND NON-DETERIORATED PATIENTS. H. A. PASKIND and M. BROWN, Am. J. Psychiat. **96**:65 (July) 1939.

The frequency of epileptic seizures was studied in 317 nondeteriorated, noninstitutionalized epileptic patients. The conclusion is drawn that "seizures are significantly less frequent in such a group than they are in deteriorated, institutional patients."

JAHR, Omaha.

CELL MINERALS IN AMAUROTIC FAMILY IDIOCY, TUBEROUS SCLEROSIS AND RELATED CONDITIONS, STUDIED BY MICROINCINERATION AND SPECTROSCOPY: EXAMPLES OF DEGENERATIVE AND OF NEOPLASTIC CELL DISEASE. L. ALEXANDER and A. MYERSON, Am. J. Psychiat. **96**:77 (July) 1939.

Active cell growth, whether neoplastic or inflammatory, is characterized by an increase in heat-resistant mineral ashes in the tissues. Cell changes of a degenerative nature, on the other hand, show an appreciable diminution of these mineral elements. This paper concerns itself with a study of two antithetic pathologic conditions: amaurotic family idiocy, representing the degenerative process, and tuberous sclerosis, representing the proliferative neoplastic process. The results of the ash determinations follow:

| | Normal | Amaurotic Family Idiocy | Tuberous Sclerosis |
|---|---|---|---|
| Silver | 0.0024 | 0.0150 | 0.025 |
| Copper | 0.0078 | 0.017 | 0.023 |
| Iron | 0.14 | 0.13 | 0.065 |
| Sodium | 1.6 | 0.27 | 0.46 |
| Magnesium | 0.45 | 0.10 | 0.15 |
| Potassium | 0.030 | 0.009 | 0.015 |
| Calcium | 0.12 | 0.057 | 0.22 |
| Phosphorus | 1.3 | 0.65 | 1.60 |

In instances of mongolian idiocy the mineral ashes of the brain showed no appreciable variation from the normal.

JAHR, Omaha.

CONVULSIVE STATES WITH EVIDENCE OF BRAIN HEMIATROPHY. L. CASAMAJOR and R. W. LAIDLAW, Am. J. Psychiat. **96**:165 (July) 1939.

Nine cases of convulsions in childhood are discussed. Roentgenographically, all the children showed thickness of the skull and enlargement of the sinuses. In every one of these children, the authors state, one side of the cerebrum did not grow as fast as the other, and this lack of growth was the result of localized injury or disease. The etiologic factors were traumatic, inflammatory or vascular.

JAHR, Omaha.

TREATMENT OF EPILEPSY WITH SODIUM DIPHENYL HYDANTOINATE. O. P. KIMBALL, J. A. M. A. **112**:1244 (April 1) 1939.

One of the complications observed in treating a large number of epileptic patients with sodium diphenyl hydantoinate (dilantin N. N. R.) was the occurrence of hyperplasia of the gums. This was often so marked as to suggest scurvy, and the ascorbic acid content of the blood was found to parallel the degree of gingival hyperplasia. This is not a contraindication to the use of dilantin for epilepsy, but it shows the need of parallel effort to raise the vitamin C content of the body. No other symptoms of scurvy were seen.

HEERSMA, Kalamazoo, Mich.

CONVULSIONS IN CHILDHOOD. M. G. PETERMAN, J. A. M. A. **113**:194 (July 15) 1939.

Peterman reviews 1,000 cases of convulsions in childhood, classifying them according to the causes in the different age groups. In the entire group, acute infections, epilepsy and cerebral injuries sustained at birth were the commonest causes. Injury incurred at birth was by far the most frequent in those under 1 month of age; infections in those between 1 month and 3 years, and epilepsy in those between 3 and 10 years. The less common causes are given with their relative frequency. The treatment for the common types is described.

This classification is intended to facilitate a thorough search for the causes of every convulsion and the prevention of injury to the child from the episode.

HEERSMA, Kalamazoo, Mich.

NEUROGENIC TUMORS OF THE SYMPATHETIC NERVOUS SYSTEM IN CHILDREN: REPORT OF THREE CASES OF SURVIVAL FOR A YEAR OR LONGER. F. H. WRIGHT and B. H. PAIGE, J. Pediat. **14**:137 (Feb.) 1939.

The majority of malignant tumors in the region of the adrenal glands are composed of embryologically young cells derived from the sympathetic nervous system, which metastasize so readily as to be almost invariably fatal. To these neoplasms the terms "neurocytoma," "neuroblastoma," "sympathogonioma" and "sympathicoblastoma" have been applied. Ganglioneuromas, tumors of similar origin but more highly differentiated, are less common. They too arise from the adrenal medulla or from the ganglions of the sympathetic chain; they grow slowly and cause symptoms chiefly through occupancy of space and pressure on neighboring structures. Early recognition of ganglioneuromas followed by surgical extirpation offers an extremely favorable prognosis. Three cases of neurogenic tumors of the sympathetic nervous system in children are reported. Two of the children are alive, with no evidence of recurrence or metastasis, one year after discovery of a large pelvic ganglioneuroma in 1 child and after discovery of a thoracic ganglioneuroma in the other. The third child is still living, six years after removal of a sympathicoblastoma, but retains the original signs and symptoms of compression of the spinal cord. Surgical removal followed by radiation therapy is the suggested treatment.

RAUH, Cincinnati.

FACTORS INFLUENCING THE RELATION OF CONVULSIONS AND HYPERTHERMIA. M. E. WEGMAN, J. Pediat. **14**:190 (Feb.) 1939.

Convulsions occurring in apparently normal healthy children at the onset of an acute infection have been attributed either to hyperprexia or to toxemia. If hyperpyrexia is the cause, the sudden rise in temperature may be responsible for the convulsions which occur only at the onset of the infection. To test the validity of this observation, experimental studies were carried out on cats of varying age. Increases in body temperature were produced over varying periods of time, and the animals were observed for convulsions. A large percentage of the kittens subjected to a rapid rise in temperature had convulsions. Adult cats under similar circumstances had convulsions much less frequently. When the temperature rise was slow and gradual, convulsions were rare, even though a considerable elevation was reached. Neuropathologic changes were found to be different for rapid and slow elevation, but no changes peculiar to convulsions were demonstrated.

RAUH, Cincinnati.

SUBDURAL HAEMATOMA. D. W. C. NORTHFIELD, Proc. Roy. Soc. Med. **32**:1200 (Aug.) 1939.

A 16 month old boy was admitted to the hospital with the complaint that for eight months he had been fretful and frequently screamed, that on one occasion he

had what was thought to have been a convulsion and that once he had become stiff and remained so for fifteen minutes. He had vomited several times and had lost weight. During two weeks the circumference of the head increased 2 cm., and the anterior fontanelle bulged. Lumbar puncture revealed a faintly yellow fluid under increased pressure. The fluid contained no excess of cells; the total protein content was 30 mg. Puncture of the right ventricle revealed a heavily blood-stained fluid. It was obtained at a depth of 3 cm. The left ventricle was not entered. On puncturing the anterior fontanelle dark blood-stained fluid was obtained on the right side, between depths of 0.5 and 4 cm. from the skin. About 100 cc. of fluid was aspirated from the right side and a small quantity of air injected. A roentgenogram showed the air to be in the subdural space. Notes on the progress of the patient and the subsequent course of the lesion accompany the report.

WILLIAMSON, New Orleans.

PNEUMOCOCCAL MENINGITIS REFRACTORY TO M & B 693. D. COURT, Proc. Roy. Soc. Med. **32**:1206 (Aug.) 1939.

A boy aged 14 months was admitted to the hospital with a history of fever for four days, respiratory distress for three days and vomiting once on the day of admission. The child was obviously ill. He was slightly cyanosed, and his throat was red. A few rales were heard in both midzones of the lungs posteriorly, and the liver was easily palpable. Type IV pneumococci were obtained from the sputum on direct typing. The child was given sulfapyridine (2-[para-aminobenzenesulfonamido]-pyridine; preparation used, M & B 693 tablets) within two hours after admission, and he improved for the next two days. However, on the third day the temperature rose high, and the child's condition appeared worse. In view of the nondevelopment of clinical and roentgen evidence of bronchopneumonia and because the fontanelle was tense, lumbar puncture was performed. An opalescent fluid was obtained which swarmed with pneumococci type IV, and 80,000 units of homologous antiserum was given intramuscularly. In spite of all treatment, death occurred on the tenth day of hospitalization. The account is accompanied by a table showing the results of the frequent examinations of the spinal fluid and the pathologist's report of the autopsy.

WILLIAMSON, New Orleans.

PSEUDOPARALYSES IN INFANCY. M. L. BABONNEIX, Arch. de méd. d. enf. **42**:609 (Oct.) 1939.

In the presence of flaccid paralysis with onset more or less brusque, the medical attendant naturally thinks first of acute anterior poliomyelitis and directs his efforts accordingly. If, later on, massive amyotrophic sequelae appear, his early suspicions are confirmed.

While in most cases such an order is observed, there are in childhood invasions concerned with an undetermined neurotropic virus rather than with the common etiologic factor in infantile paralysis. Beriel and Devic, in 1925, and Verger and Cruchet, in 1926, published reports of such observations.

The author records 4 clinical cases in which on first examination the classical syndrome of infantile paralysis appeared but in which later the disease was placed in the category of radiculoneuritis with albuminocytologic dissociation.

AMESSE, Denver.

GENESIS OF INFANTILE TETANY. A. DORDI, Lattante **10**:363 (Sept.) 1939.

Determinations of calcium, potassium, phosphorus and guanidine were made on the blood of 9 infants with tetany; in 3 of the cases determinations were also made after the tetany was cured. In each case, both during active tetany and after cure the guanidine of the blood was within normal limits, i. e., between 0.2

and 0.3 mg. per hundred cubic centimeters; the potassium of the blood serum was also within normal limits. The conclusion is drawn that guanidine does not have any pathogenic influence in the development of infantile tetany.

HIGGINS, Boston.

ENCEPHALOCELE. P. ORSINI, Med. inf., Rome **10**:266 (Sept.) 1939.

A boy of 13 months had hydrocephalus and a hydroencephalomeningocele near the right occipital-parietal suture.

HIGGINS, Boston.

## Diseases of the Genitourinary Tract

ELECTROCARDIOGRAPHIC CHANGES IN ACUTE HEMORRHAGIC NEPHRITIS. R. D. WILLIAMS, Bull. Johns Hopkins Hosp. **65**:434 (Dec.) 1939.

Serial electrocardiograms were taken in 15 cases of acute glomerular nephritis. In 10 cases changes were observed, chiefly flattening and inversion of the T waves in one or more leads. There was no correlation between these changes and the signs of cardiac and renal insufficiency.

LYTTLE, New York.

THE ULTIMATE PROGNOSIS OF NEPHRITIS IN CHILDHOOD. J. M. CASS, Arch. Dis. Childhood **14**:137 (June) 1939.

A hundred and twenty patients with nephritis, who had been in the Children's Hospital, Birmingham, England, were examined and, on the basis of the results of urinalyses and chemical studies of the blood, were grouped as having (1) healed, (2) latent, (3) active and (4) terminal nephritis. Those whose nephritis was in the latent stage were usually free from symptoms and usually had normal blood, but a few exceptions were noted. There was no change in the protein components of the plasma which could be considered typical of any one stage of the disease; these components were abnormal in all the patients with nephritis in the active or subacute stage.

Eighty-eight patients with acute hemorrhagic nephritis who were first admitted during the initial attack were examined six months to five years after the onset. The mortality in the acute attack was 3.4 per cent. Two patients were found to have nephritis in the terminal stage with hypertension. In 32 per cent of the patients the disease was in the latent stage, and in 64 per cent the renal lesions were healed. The estimated ultimate mortality was 27 per cent.

The liability of the disease to become chronic was not affected by removal of the apparent focus of infection, usually infected tonsils, in the acute stage of the disease, nor was it related to the severity of the initial attack or to the length of either the confinement to bed or the dietary treatment in the initial attack.

Fourteen patients who were first seen when their nephritis was in the active or subacute stage were examined. The actual mortality was 50 per cent, and the probable ultimate mortality will be at least 79 per cent. Ten patients having nephritis with insidious onset have been examined. Four have recovered and the remaining 6 are unlikely to recover.

KELLY, Milwaukee.

SARCOMA OF THE PROSTATE IN CHILDREN. I. FRASER, Irish J. M. Sc., July 1939, p. 330.

Fraser reports fatal sarcoma of the prostate in a boy 3 years of age, who was brought for examination because of acute urinary retention. A large cystic mass was palpated in the abdomen, and rectal examination disclosed enlargement of the prostate. The prostate was removed, but the boy died two days after operation. The mass was a rhabdomyosarcoma.

C. E. SNELLING, M.B., Toronto, Canada.

TREATMENT OF CRYPTORCHIDISM WITH EXTRACT OF ANTERIOR LOBE OF PITUITARY. H. J. KRAETSCH, München. med. Wchnschr. **86**:1638 (Nov. 17) 1939.

Kraetsch treated cryptorchidic patients in whom operation had failed with an extract of the anterior lobe of the pituitary. The patients had their operations several years before at 4 or 6 years of age, but the testicles were either in the inguinal canals or not palpable. Of the 10 patients treated with the extract, 6 had satisfactory descent of the testicles. Nine other school children received the same treatment, and in only 1 child was it a failure. In this patient adhesions were subsequently found at operation. BRAHDY, Mount Vernon, N. Y.

TORSION OF THE PEDICLES OF OVARIAN CYSTS IN CHILDREN. J. W. MILLER, Ztschr. f. Geburtsh. u. Gynäk. **119**:336, 1939.

Miller has collected 95 cases of ovarian tumor in childhood in which the pedicle became twisted. The tumors were largely teratomas, carcinomas, cysts and parovarian cysts. They were distributed fairly evenly throughout the period from 1 to 15 years except for a slight increase at 9 and 10 years. The symptoms and complications were largely dependent on the degree of obstruction to the blood supply. The differential diagnosis must include hematometra, hematosalpinx, mesenteric or chylous cysts, dilated gallbladder, hydronephrosis, encapsulated ascites, volvulus, intussusception and pelvic abscess. ADAIR and POTTER, Chicago.

VITAMIN C CONTENT OF URINE IN INFANTS. I. GAMMO, Acta pædiat. japon. **45**:1076 (Aug.) 1939.

The vitamin C content of urine is high in breast-fed infants and low in artificially fed babies. The amount of vitamin C in the urine of a breast-fed infant is directly proportional to the amount in the mother's milk. The afternoon samples show, as a rule, higher values than the morning ones. KATO, Chicago.

FORMATION AND THERAPY OF RENAL AND VESICAL CALCULI. A. POLAK, Nederl. tijdschr. v. geneesk. **83**:4009 (Aug. 12) 1939.

In a former paper Polak showed that it is possible to produce renal and vesical calculi in rats experimentally. In the present communication he describes three experiments in which he produced renal and vesical calculi in rats and tried certain methods of treatment. His conclusions are: It is not possible to eliminate experimentally produced renal and vesical calculi (citrate stones) by adding 0.3 per cent sodium benzoate to the diet. It does appear possible to eliminate them by altering the urinary $p_H$ in the rats. It is possible to prevent the formation of vesicorenal calculi by adding 0.3 per cent sodium salicylate to the diet. It is possible to produce oxamide stones in the kidneys and bladders of young white rats by giving them 3 per cent oxamide in their food. The addition of 0.3 per cent sodium benzoate to this diet does not prevent the formation of these stones. VAN CREVELD, Amsterdam, Netherlands.

## Diseases of the Ductless Glands; Endocrinology

THE SIGNIFICANCE OF POST PRANDIAL GLYCOSURIA IN THE TREATMENT OF DIABETES MELLITUS WITH PROTAMINE INSULIN. I. M. RABINOWITCH, Ann. Int. Med. **13**:385 (Sept.) 1939.

Postprandial glycosuria occurring in persons with diabetes mellitus is of no significance provided the patients are taking protamine zinc insulin and are receiving diets high in carbohydrate and low in calories and when asscciated with normal blood sugar levels in the fasting state.

The cholesterol content of the blood plasma offers a reliable index of progress in diabetes. There is an increase of the values for plasma cholesterol in direct ratio to the increased frequency of glycosuria. READING, Galveston, Texas.

ABDOMINAL DISTENTION: A MANIFESTATION OF POSSIBLE THYROID INSUFFICIENCY IN SOME CHILDREN. GEORGE B. DORFF and BENJAMIN STOLOFF, Arch. Pediat. **56**:291 (May) 1939.

Two cases are reported.

ORR, Buffalo.

THE WATERHOUSE-FRIDERICHSEN SYNDROME. RALPH H. KUNSTADTER, Arch. Pediat. **56**:489 (Aug.) 1939.

A 12 day old boy died of acute meningococcic septicemia with bilateral adrenal apoplexy (Waterhouse-Friderichsen syndrome).

The diagnosis was made before death and confirmed at autopsy.

A review of the literature and a detailed description of the disease are presented.

ORR, Buffalo.

ADRENAL NEUROBLASTOMA. Arch. Pediat. **56**:561 (Sept.) 1939.

A case of adrenal neuroblastoma in a 5 year old boy, originating from a neurocytoma of the left adrenal gland, is presented. An area of the adrenal grew very rapidly, differentiated to neuroblast cells and metastasized widely. The metastatic cells stimulated erythropoiesis, and the biopsy specimens gave the appearance of erythroblastomatosis.

ORR, Buffalo.

PRESENT STATUS OF PROTAMINE INSULIN. HERMAN LANDE, Bull. New York Acad. Med. **15**:273 (April) 1939.

This report is based on a two year study of protamine zinc insulin in a large clinic. In only about 25 per cent of cases can diabetes be satisfactorily controlled with protamine zinc insulin alone. It has not solved the problem of the patient with severe diabetes, although the prolonged action of this form of insulin is of undoubted benefit in the treatment of the disease.

JAHR, Omaha.

THE URINARY EXCRETION OF ESTROGENIC SUBSTANCES AFTER THE ADMINISTRATION OF TESTOSTERONE PROPIONATE. RALPH I. DORFMAN and JAMES B. HAMILTON, Endocrinology **25**:33 (July) 1939.

Intramuscular injection of 20 mg. of testosterone propionate in a man resulted in a 500 per cent increase in the estrogenic activity of the urine. Administration of the substance by mouth produced no effect.

Increased estrogenic activity of the urine following administration of androgen indicates that some portion of the estrogenic output of normal men may be a result of the influence of androgen.

JACOBSEN, Buffalo.

STUDY ON DESOXY-CORTICOSTERONE. GEORGE W. THORN and HARRY EISENBERG, Endocrinology **25**:39 (July) 1939.

Experiments on bilaterally adrenalectomized dogs indicate the effectiveness of synthetic desoxycorticosterone acetate in preventing symptoms of adrenal insufficiency.

JACOBSEN, Buffalo.

THE ROLE OF THE CERVICAL SYMPATHETICS IN THE REGULATION OF THYROID AND THYROTROPIC FUNCTION. UNTO U. UOTILA, Endocrinology **25**:63 (July) 1939.

As a result of a series of experiments in which thyroid activity in rats was studied under various conditions of stimulation of the cervical sympathetic nerves (by cold) and before and after "cervical sympathectomy," it was concluded that the cervical sympathetic nerves appear to be unnecessary for histologically normal function of the thyroid.

JACOBSEN, Buffalo.

THE NEUROHYPOPHYSIS AND WATER EXCHANGE IN THE MONKEY. H. W. MAGOUN, C. FISHER and S. W. RANSON, Endocrinology **25**:161 (Aug.) 1939.

In a study of the importance of the hypothalamic innervation of the neurohypophysis for the regulation of water exchange in the monkey, a series of animals were subjected to subtemporal section of the infundibular stalk and observed for periods up to twelve weeks after operation.

In the different animals marked permanent polyuria, mild permanent polyuria, brief secondary polyuria and normal outputs of urine were encountered.

Histologic studies showed that the degree of polyuria depended on the amount of normal neurohypophysial tissue which remained proximal to the section and connected with the hypothalamus.

JACOBSEN, Buffalo.

SUCCESSFUL TREATMENT OF DIABETIC GIRLS WITH PROTAMINE ZINC INSULIN. PRISCILLA WHITE and LOVILLA WINTERBOTTOM, J. A. M. A. **112**:1440 (April 15) 1939.

In a summer camp for girls, tests were made on the second, tenth and twelfth days on 123 girls to determine the effectiveness of protamine zinc insulin. The results indicated an incidence of 94 to 96 per cent adequate control. The patients were well above the average standards for height and weight. Reactions were rare. Camp care is recommended and described briefly.

HEERSMA, Kalamazoo, Mich.

REMOVAL OF THE THYMUS. E. I. HASHIMOTO and C. B. FREUDENBERGER, J. A. M. A. **112**:1680 (April 29) 1939.

Comparing the results of surgical removal of the thymus of rats to those of roentgen irradiation as described by Shay and his co-workers, the authors found none of the changes described by them, such as delayed growth, delayed development of the testes, temporary sterility and hypophysial changes of a castrate. They attribute these changes to side irradiation of the thyroid, which produces a similar picture, and not to degeneration of the thymus.

HEERSMA, Kalamazoo, Mich.

RESPONSES OF NORMAL SUBJECTS AND OF PATIENTS WITH DIABETES INSIPIDUS TO WATER AND SALT INGESTION. H. L. WHITE and T. FINDLEY JR., J. Clin. Investigation **18**:377 (July) 1939.

The 4 diabetic patients studied failed to show within a few hours an increase in the flow of the urine in response to a large drink of water when the flow of urine preceding the drink was below maximal. After administration of a dose of 0.25 Gm. of sodium chloride in 10 per cent solution per kilogram of body weight, 3 of the 4 patients failed to show any increase in chloride output within five hours, while 1 showed the normal response of an increased urinary chloride output. Further studies of the effects of pitressin on urinary excretion of chloride were made with these patients and with normal subjects.

The authors believe that there is no justification for the view that diabetes insipidus is primarily a disturbance of the processes of exchange of water and salt between tissues and blood.

GUEST, Cincinnati.

THE WATERHOUSE-FRIDERICHSEN SYNDROME: REPORT OF A CASE WITH AUTOPSY FINDINGS. SAMUEL A. LEVINSON, J. Pediat. **14**:506 (April) 1939.

The disease known as the Waterhouse-Friderichsen syndrome is accompanied by sudden onset of malaise, diarrhea, fever, rapid pulse, cyanosis, purpuric spots on the skin, lethargy, coma and death. It is usually fatal from twenty-four to forty-eight hours after the onset of symptoms. The cause is not definitely known, although many believe that the disease may be associated with a bacteremia or a toxemia. The essential pathologic findings consist of massive bilateral hemorrhages

in the adrenal glands with purpuric spots in the skin. The autopsy observations in a case of the disease are reported.

RAUH, Cincinnati. [FROM THE AUTHOR'S CONCLUSION.]

HYPERCALCIFICATION, -CALCEMIA AND -LIPEMIA IN CHICKENS FOLLOWING ADMINISTRATON OF ESTROGENS. W. LANDAUER, C. A. PFEIFFER, W. U. GARDNER and E. B. MAN, Proc. Soc. Exper. Biol. & Med. **41**:80 (May) 1939.

Estradiol benzoate injected into 6 to 7 month old cocks decreased the size and produced a typical capon-like appearance. There was deposition of new bone throughout the epiphyses and diaphyses, the walls being uniformly thickened, and the trabeculae of the spongy bone invaded the marrow. A definite relation was found between the daily dose of estradiol benzoate and the extent of new calcification. The level of serum calcium rose. There was also a great increase in the lipid constituents of the serum. Changes in the liver and kidney were also observed.

HANSEN, Minneapolis.

THE THYMUS GLAND IN INFANTS AND CHILDREN. HARLOW R. CONNELL, West Virginia M. J. **35**:273 (June) 1939.

The thymus gland is rather fully discussed from the standpoints of size, growth, anatomy, histology, physiology, symptomatology, pathology, relation to other members of the endocrine system, diagnosis and treatment.

The literature is freely cited.

The author's conclusions are:

Much remains to be learned of the physiology of the thymus.

The width of the gland has no significance. The thickness is of importance.

The dangers and frequency of enlargement of the thymus are greatly exaggerated.

Lateral views provide the only true roentgen diagnosis.

Sudden "anesthetic deaths" are due to temporary engorgement.

Artificial respiration is useless. Mouth to mouth inflation is helpful.

SHAWKEY, Charleston, W. Va.

CLINICAL APPLICATION OF THYREOTROPHIC HORMONE. K. S. HARRISON, M. J. Australia **1**:681 (May 6) 1939.

Harrison gave four daily doses of 1,000 units of thyrotrophic substance to 5 patients suffering from different types of thyroid insufficiency. Two patients in whose cases a subnormal metabolic rate was associated with primary pituitary deficiency showed elevation of the basal metabolic rate and a pronounced fall in the level of cholesterol in the blood after administration of the hormone. One whose thyroid had been removed gave no response in either the basal metabolic rate or the value for blood cholesterol. Of 2 patients with spontaneous hypothyroidism, 1 exhibited no increase in the metabolic rate but a pronounced fall in the value for blood cholesterol and the other only a slight elevation in metabolic activity and a small reduction in the level of blood cholesterol. Explanations for the disparity between the changes in the level of blood cholesterol and the basal metabolic rate are offered. The author believes that the conditions which provide the only fertile field for prolonged therapy with thyrotrophic hormone are those in which there is secondary hypothyroidism due to primary pituitary insufficiency. It can be seen that a test dose of thyrotrophic substance will help in distinguishing between primary thyroid insufficiency and hypothyroidism secondary to pituitary insufficiency.

GONCE, Madison, Wis.

TREATMENT OF DIABETES WITH PROTAMINE ZINC INSULIN. R. BOULIN, Presse méd. **47**:541 (April 12) 1939.

Boulin presents 100 cases of diabetes, comparing the results obtained with ordinary insulin and those obtained with protamine zinc insulin. The ages of

his patients ranged from 10 to 80 years. With fewer units and fewer injections, the protamine zinc insulin equaled or bettered the results obtained with ordinary insulin. Glycosuria, however, could not be controlled as well with protamine zinc insulin. No local or general complications were encountered in the series.

DAFFINEE, Boston.

WATERHOUSE-FRIDERICHSEN SYNDROME. F. PONTIERI, Med. ital. **20**:231 (May 31) 1939.

An 8 month old child, previously healthy, suddenly became ill with fever and generalized cutaneous hemorrhages, showed signs of collapse and died in twelve hours. Autopsy showed bilateral hemorrhages of the adrenal glands. The glands were transformed into hemorrhagic sacs with total destruction of the medulla and almost total destruction of the cortex. There were marked hyperplasia of the thymus, the lymphatic system (especially that of the tongue), the intestine and the spleen. Catarrhal inflammation of the pharynx, larynx, trachea and bronchi was present. The lower pulmonary lobes were atelectatic. There were congestion of the leptomeninges and cloudy swelling of the myocardium, liver and kidneys. Histologic examination of the tissues is reported on.

MARTOCCIO, Utica, N. Y.

HYPOGLYCEMIC ACTION OF INSULIN ADDED TO TANNIC ACID. G. TOMMASEO and C. BERTOLLO, Riv. di clin. pediat. **37**:535 (June) 1939.

Observations were made on rabbits and on nondiabetic children. When insulin mixed in a solution of 2 per cent tannic acid was injected, the lowering of the blood sugar curve was slower and took place over a longer period than when insulin alone was injected.

HIGGINS, Boston.

WATERHOUSE-FRIDERICHSEN SYNDROME. G. CAREDDU, Riv. di clin. pediat. **37**: 784 (Sept.) 1939.

The Waterhouse-Friderichsen syndrome occurs in infants and young children, is rapidly fatal and is characterized by extensive hemorrhage into the adrenal gland (apoplexy of the adrenal), purpura and lymphatic hyperplasia, especially of the thymus, spleen and lymph glands.

The cases of 3 children aged 3 months, 6 months and 3 years respectively are reported, with necropsies. In none of the 3 cases were meningococci or other causative bacteria found.

HIGGINS, Boston.

ENLARGEMENT OF THE THYMUS GLAND. ALEIXO DE VASCONCELLOS, Arch. de pediat. d. Uruguay **11**:1075 (March) 1939.

A common case of enlarged thymus with respiratory distress is presented. The patient was a child 40 days of age. Confirmatory roentgenograms were taken, and roentgen therapy was used, with satisfactory results. Discussions on this subject are offered together with some quotations from the foreign literature.

SOTO, Habana, Cuba.

ANTI-ENDOCRINE GLAND PRECIPITINS IN VARIOUS DISTURBANCES OF THE INTERNAL SECRETIONS OF MAN. C. PICADO and W. ROTTER, Rev. méd. latino-am. **24**:765 (May) 1939.

The authors briefly summarize their study of precipitins in the blood serum produced by emulsions of various endocrine glands. It was found that the precipitin in the serum varies with the different antigen used and that it tends to increase with the age of the subject. The precipitins of patients with toxic and colloid goiter, myxedema, cretinism, nanism and disorders of the hypophysis, testes and

ovary were studied. Although the data are difficult to interpret, it can be stated that the precipitin titer is not in direct relation to the hypofunction or hyperfunction of the corresponding gland; the relative titer between the different precipitins signifies a disturbance of function of one of the various endocrine glands. Because of the functional synergy of the internal secretions, it is probable that a disturbance in one is reflected in the others. DWYER, Kansas City, Mo.

## Diseases of Muscles, Bones, Joints and Lymph Glands

THE ANTERIOR AND POSTERIOR "NOTCH" SHADOWS SEEN IN LATERAL ROENTGENOGRAMS OF THE VERTEBRAE OF INFANTS: AN ANATOMIC EXPLANATION. G. WAGONER and E. P. PENDERGRASS, Am. J. Roentgenol. **42**:663 (Nov.) 1939.

Wagoner and Pendergrass present anatomic data for the interpretation of the anterior and posterior "notch" shadows seen in lateral roentgenograms of the vertebral bodies of newborn and older infants.

The posterior "notch" is real and may be seen at any age, though it is relatively larger in infancy. The "notch" seen in the lateral roentgenogram of the human vertebra is produced by an actual indentation of the posterior cortical wall at the site of entrance of a vein or of emergence of an artery. The anterior "notch" is apparent in the lateral roentgenogram but is not real. It is due to a definite structural difference between the central and the superior and the inferior zone of the vertebral body; also the anterior portion of the central zone differs from the posterior. These structural differences lead to a differential of roentgen ray permeability, producing shadows which appear as a central band of lessened density extending horizontally from anterior to posterior and an apparent "notching" of the central portion of the anterior wall when viewed laterally. In addition to the difference in structure of the vertebral body, the vascular content of the body accentuates "notching" anteriorly. The anterior "notching" disappears with ossification of the anterior and lateral walls of the body and replacement of the blood sinusoidal area by bone marrow. SQUIRE, Chicago.

OSTEOPSATHYROSIS (FRAGILITAS OSSIUM). H. H. MCGARRY, Canad. M. A. J. **41**:354 (Oct.) 1939.

Fragilitas ossium is reported in a day old baby. There was no family history of similar trouble. At birth the baby showed numerous fractures as well as bony deformities. On the sixth day the baby suddenly became cyanosed and died. The observations at autopsy seemed to support the view of Weber that osteogenesis imperfecta is a condition of arrested development of bone rather than one of bone dystrophy.

Analysis of the bone ash showed that the ash was 27.3 per cent of the fat-free bone instead of the normal 40.7 per cent. MOORE, Omaha.

MARBLE BONE DISEASE (ALBERS-SCHÖNBERG DISEASE) IN CHILDREN. A. ALBRECHT and O. GEISER, Ann. pædiat. **153**:84 (May) 1939.

This is a report of 2 cases of the malignant infantile form of marble bone disease. The patients were a girl of 15 months and a boy of 7½ years, first cousins. The parents of one child were blood relations. Both children showed grave changes of the skeletal system—i. e., the generalized severe sclerosis of all the bones, with changes in the shape of the skull and the long bones, typical of this disease. Numerous pictures illustrate the bony changes, and special features peculiar to these 2 cases are pointed out. Both patients had hydrocephalus and optic atrophy; 1 had in addition palsy of the right side of the face, severe progressive anemia with extramyeloid regeneration of the blood and enlargement of the liver and spleen.

The clinical picture and the differential diagnosis of marble bone disease are discussed. The infantile form can be clearly marked off from the more benign forms of adult age. Both forms never occur in the same family. Harnapp's classification is rejected. The differential diagnosis of the infantile form does not offer any difficulties, but it is not easy to mark off the second group from cases of osteosclerosis following primary disease of the blood. The pathologic changes mentioned in the literature and the results of metabolic investigations, as well as theoretic conceptions of the disease, are briefly touched on.

FROM AUTHORS' SUMMARY.

MALACIA OF THE SECOND CUNEIFORM BONE. G. KÜNTSCHER, Röntgenpraxis **11**:94 (Feb.) 1939.

Following a brief but useful review of some of the general and special aspects of osteochondritis deformans, Küntscher presents a rare case, in which the lesion was located unilaterally in the second cuneiform bone of the left tarsus.

McCUNE. New York.

BONE CHANGES IN A CRETINOID BOY. D. PAULIAN and E. HERKOVITS, Röntgenpraxis **11**:181 (March) 1939.

A physically well developed but mentally retarded 15 year old boy is presented, who exhibited physical features of congenital hypothyroidism. Serologic examination revealed syphilis. Roentgenographically there were demonstrated: (1) bilateral hypoplasia of the middle phalanges of the little fingers, such as is seen in mongolism; (2) right-sided humerus varus with premature fusion of the proximal epiphysis of the humerus, and (3) local atrophy and a focal defect of the neck of the humerus that had resulted in a pathologic fracture.

McCUNE, New York.

DIAGNOSIS OF TUMORS OF THE SKULL (XANTHOMA AND CHOLESTEATOMA OF THE CALVARIUM). H. BADE, Röntgenpraxis **11**:223 (April) 1939.

The differential diagnosis of circumscribed roentgen defects of the calvarium includes angioma, dural endothelioma, glioma, metastasis of a malignant neoplasm, inflammatory disease, solitary cyst, xanthoma and cholesteatoma. With the exception of the last two, it is usually possible to distinguish the various possibilities on the basis of roentgen examination combined with a knowledge of the clinical features of the lesion. Xanthoma of the skull is a comparatively common phenomenon; in contrast with the familiar secondary cholesteatoma of otitic origin, primary cholesteatoma is a rare lesion in any part of the skull, doubly so in the calvarium. However, the two types of process produce identical roentgen features when they appear in membranous bone. In most instances, as in those that furnish material for this report, histologic examination is required to distinguish between them. The 2 cases that are reported are those of a 2½ year old child with xanthomatosis and a 31 year old adult with a cholesteatoma of the calvarium.

McCUNE, New York.

LERI'S MELORHEOSTOSIS: A CASE EXHIBITING BILATERAL DISPOSITION OF THE HYPEROSTOTIC AND OSTEOSCLEROTIC LESIONS IN THE PELVIS AND THE LOWER EXTREMITIES. K. J. BURY, Röntgenpraxis **11**:292 (May) 1939.

To the 27 reported cases of monomelic flowing hyperostosis another is added. The patient, a woman, was 35 years of age when the diagnosis was made; the time of onset of the illness was not determined. The occurrence in this case and in others of lesions in both halves of the skeleton demonstrates that the criterion of unilaterality cannot be applied in the diagnosis of the disease.

Bury reviews the clinical and roentgen manifestations of this rare entity, includes a list of the reported cases and supplies a comprehensive bibliography of the subject to 1939. The disease has been recognized at least five times in children.

McCUNE, New York.

ISCHIOPUBIC OSTEOCHONDRITIS. W. WILKEN, Ztschr. f. Kinderh. **61**:127 (June 6) 1939.

In 1925 van Neck reported 2 cases of ischiopubic osteochondritis, and several cases were reported subsequently. The paucity of case reports may indicate rarity or insufficient recognition of the condition. The causes are uncertain. Overexertion and injury may be factors. As a general rule, only children 8 to 12 years old are affected.

The clinical onset may be gradual or sudden, with unilateral pain in the hip or groin. Limping and increased fatigability are present. There may be pain on pressure over the ischium or over the pubis; frequently also there are slight redness and swelling. The clinical course is benign, and recovery usually occurs without special treatment.

Roentgen examination shows a rounded, usually unilateral enlargement, greater than normal, at the junction of the ischium and the inferior ramus of the pubis. A small lighter area may be seen within the enlarged area.

The author reports a case. Subfebrile elevations of temperature were observed, a feature not reported previously.

SIEMSEN, Chicago.

## Skin Diseases; Allergy

CONTROLLED INSULIN SHOCK TREATMENT OF ASTHMATIC CHILDREN. HERMANN VOLLMER, Arch. Pediat. **56**:223 (April) 1939.

Seven asthmatic children were treated with a course of fifteen to twenty-five injections of insulin. Severe symptoms of shock were controlled by regulated doses of insulin or by administration of small amounts of sugar at the onset of such symptoms.

Most children were at least temporarily benefited, and the asthmatic attacks were frequently relieved by insulin.

This effect is ascribed to a secondary endogenous production of epinephrine following the administration of insulin. As the influence of insulin continues, compensatory hyperfunction of the adrenal system may result, which benefits the asthma.

In severe cases epinephrine should be replaced by insulin in controlling asthmatic attacks. The author presents the theory that continuous administration of epinephrine may aggravate the asthma.

ORR, Buffalo.

EXANTHEM SUBITUM. GEORGE E. STAFFORD, Arch. Pediat. **56**:246 (April) 1939.

Two cases are reported to substantiate the evidence that neurologic signs may occur during the course of the disease.

ORR, Buffalo.

ANESTHESIA AND THE ACRODYNIA PATIENT. E. FULTON, H. LIVINGSTONE, C. MORRISON and M. ROSS, Arch. Pediat. **56**:481 (Aug.) 1939.

Seventeen children with acrodynia underwent 26 operations for various conditions and under anesthesia induced with various agents. There were 4 postoperative deaths. Three of these were among the 4 patients who were in very poor condition while under anesthesia. This would suggest rapid termination of operation and anesthesia in such cases. It also raises the question of the advisability of elective operation for such patients.

ORR, Buffalo.

A Slowly Absorbed Gelatin Epinephrine Mixture. W. C. Spain, M. B. Strauss and A. M. Fuchs, J. Allergy **10**:209 (March) 1939.

A 1 to 500 epinephrine-gelatin mixture is described. Its purpose is to provide slow absorption of the epinephrine in the treatment of chronic asthmatic patients. It is nontoxic, nonantigenic and readily administered. It has an advantage over the preparation described by Keeney in that the syringe used for administering it need not be dry.

Hoyer, Cincinnati.

Slow Epinephrine in the Treatment of Chronic Asthma. John A. Murphy and C. A. Jones, J. Allergy **10**:215 (March) 1939.

A series of 9 cases of chronic asthma in which "slow epinephrine" was used is reported. The results were gratifying in all cases. The amount of epinephrine used was decreased, and the effect of the dose lasted over a longer period.

Slow epinephrine is a 1 to 500 solution of epinephrine in purified peanut oil.

Hoyer, Cincinnati.

Heterophile Antibody Determinations in 148 Allergic and 107 Nonallergic Persons. Marshall W. Sinclair and J. Warrick Thomas, J. Allergy **10**:228 (March) 1939.

The article is difficult to abstract in detail. The authors believe that the evidence obtained may be interpreted in either of two ways: "that there is no constant relationship between the allergic state, active or quiescent, and the heterophile antibody titer; or, that the possibility of a reduced titer during the acute allergic phase may be of significance and deserves further investigation."

The history of administration of serum frequently agrees with a high titer.

Hoyer, Cincinnati.

The Relief of Severe Intractable Bronchial Asthma with Cyclopropane Anesthesia. Nathanial E. Meyer and Seymour Schotz, J. Allergy **10**: 239 (March) 1939.

A case reported in which cyclopropane was used with success. The value of cyclopropane is in the rapid induction of anesthesia, which prevents struggling and any undue strain on the heart, and the quantity of oxygen used aids in overcoming the anoxemia.

Hoyer, Cincinnati.

Unusual Reactions to Slow Epinephrine. Jack Cohn, J. Allergy **10**:459 (July) 1939.

Four cases are reported in which reactions occurred after the use of 1 cc. of 2 mg. epinephrine crystals in peanut oil injected intramuscularly.

The symptoms consisted of nausea, vomiting, increased dyspnea and edema of the forearm.

Hoyer, Cincinnati.

The Anti-Acrodynic Properties of Certain Foods. Howard A. Schneider, J. Katherine Ascham, Blanche R. Platz and H. Steenbock, J. Nutrition **18**:99 (July) 1939.

These Wisconsin investigators have assayed fifty-two foodstuffs for their antiacrodynic activity (antidermatic factor, vitamin $B_6$), using the rat as the experimental animal. Their data show that certain vegetable fats are extremely potent sources of antiacrodynic activity; fruits and vegetables are poor; meats and fish are fair and seeds, legumes and cereals are relatively rich. Yeast shows about the same potency as the cereals. Lard is actually six times as potent as yeast.

Fredeen, Kansas City, Mo.

TREATMENT OF HEMANGIOMAS AND LYMPHANGIOMAS IN INFANTS AND CHILDREN. FRED M. HODGES, L. O. SNEAD and R. A. BERGER, Virginia M. Monthly **66:** 263 (May) 1939.

The term "nevus" includes two groups of pathologic entities: lesions of epidermal origin, such as the pigmented nevus, and lesions of mesodermal origin, such as hemangioma and lymphangioma. The first group is relatively radioresistant, but the second group is radiosensitive. Even in the group of mesodermal lesions there are gradations of radiosensitivity. The capillary hemangiomas (port wine stains) are the most difficult to treat radiologically, but good results may be obtained if they are treated in the first year. The cavernous hemangiomas ("strawberry" type) may be superficial or deep. Radium is most applicable to the superficial type and roentgen rays to the deep. Some respond best to roentgen therapy followed by radium. Lymphangiomas are similar histologically and in other ways to cavernous hemangiomas and like them respond to radiant energy. Exceptions to this are the lymphangiomas which are made up of large single cysts. These are not radiosensitive. In the treatment of various types of radiosensitive vascular tumors, early application of roentgen rays and radium gives a quicker and more pleasing cosmetic result than does later application. The treatment should preferably be given during the first few weeks or months of life.

STONE, Richmond, Va.

INFANTILE ACRODYNIA. H. C. DAVIS, West Virginia M. J. **35:**277 (June) 1939.

The cause of acrodynia has not been established. There are numerous theories. There seems to be a relation to infections of the upper respiratory tract. It occurs in children aged from 8 months to 4 years. It is independent of sex or social status. The history is sketched. References to the literature are made.

The clinical picture is classic. "Raw beef hands and feet" are the most typical symptom and may go on to ulceration and even to gangrene.

A case history is presented.

SHAWKEY, Charleston, W. Va.

A CASE OF PIGMENTED ECZEMA WITH MACROCYTIC ANEMIA. NORMAN BURGESS and CATHERINE MACLAREN, Brit. J. Dermat. **51:**207 (May) 1939.

The authors report the case of a boy aged 13 on whom the hyperpigmented patches persisted for months after the eruption had cleared. It was thought that hepatic deficiency, indicated by the absence of antianemic substances, was responsible for the excessive pigmentation formed in the cutaneous lesions.

RATTNER, Chicago. [ARCH. DERMAT. & SYPH.]

PHYSIOTHERAPY IN FURUNCULOSIS. JEAN MEYER, Brit. J. Phys. Med. **2:**72 (March) 1939.

The author advocates the use of roentgen and short wave therapy for recurring and severe types of furuncles and carbuncles. A technic of treatment is outlined. A few favorable case histories are given.

HARTMAN, Cleveland.

HERPES SIMPLEX. F. M. BURNET and DORA LUSH, Lancet **1:**629 (March 18) 1939.

Herpes antibody in human serums can be titrated on the chorioallantois. With few exceptions human serums either contain no herpes antibody or are highly active against the virus. There is no relation between susceptibility to clinical poliomyelitis and absence of herpes antibody. Herpes virus could not be demonstrated post mortem in the gasserian ganglions of persons with high titer herpes antibody. Aphthous stomatitis in infancy is the common manifestation of primary infection with herpes virus. Primary herpes is an infective disease spread by droplet infection or by salivary contamination, particularly in children aged from 1 to 3 years.

As a working hypothesis the authors adopt the view that, once maternally transmitted immunity has been lost, there is a period roughly from 9 months to perhaps 5 years of age during which the child is readily susceptible to infection of the buccal mucosa by herpes virus. Once infection has been acquired, the virus persists in certain cells throughout life and provokes its characteristic manifestation, labial herpes, when conditions are suitable. LANGMANN, New York.

HERPES SIMPLEX: A NEW POINT OF VIEW. F. M. BURNET and S. W. WILLIAMS, M. J. Australia **1**:637 (April 29) 1939.

Herpes simplex is primarily an acute, often febrile disease of infancy or early childhood, of which the characteristic lesion is vesicular (aphthous) stomatitis, often with secondary involvement of the lips, face or fingers. The primary lesion usually heals within a week or two, and antibody develops in the blood. In all probability the child is thereafter immune to herpetic stomatitis. The virus, however, persists somewhere in the body, probably for the whole of life, always apt under a sufficient stimulus (the necessary intensity of which varies greatly from one person to another) to break out into local activity. Infection of infants may be from a virus liberated from a recurrent lesion in an adult or from a primary lesion in another child. So far as the authors know, no other virus has established this type of almost symbiotic existence in man, but it is of great interest that two viruses which are clearly related to herpes virus have acquired a similar relation with two other mammalian species, namely, the virus of pseudorabies of American swine and the B virus of monkeys. GONCE, Madison, Wis.

SYNDROME OF CRIST-SIEMENS (ANHYDROSIS WITH HYPOTRICHOSIS AND ANODONTIA). A. BARCAGLIA, Med. ital. **20**:357 (July) 1939.

A 3 year old child with two teeth which erupted at the age of 10 months is described. The teeth were conical and resembled those of a pig. They were situated where the upper central incisors are supposed to be located. Roentgen examination showed only four dental outlines in the upper jaw and none in the lower jaw. The mother lacked a lower lateral incisor on the left. All the others in the family presented normal teeth. The child's Wassermann reaction was negative. The skin of the limbs, neck and face was coarse, dry and thin. The child had never been seen to sweat. The summer heat was poorly tolerated, and the child would try to cool the hot skin by resting on the stone pavements.

There was a slight degree of hydrocephalus. The hair was dry, sparse, very fine, fragile and very pale blond. The eyebrows and eyelashes were almost absent. The nose was of the saddle type. The child was fed on liquid food. Photographs and roentgenograms of the skull are presented. MARTOCCIO, Utica, N. Y.

TREATMENT OF ASTHMA IN INFANCY. CAUPOLICAN R. CASTILLA, Rev. méd. latino-am. **24**:891 (June) 1939.

On the basis of a long experience in the treatment of asthmatic children and the study of the allergic factors that intervene in this disease, the author gives a brief summary of the fundamental causes of asthma and the various therapeutic methods in use today. The influence of heredity on asthma is noteworthy, and it is necessary to study the individual patient to discover the possible predisposing causes, such as tuberculosis, hereditary syphilis, hepatism, autointoxication, focal infection and endocrine disorders.

Among the determining causes of the asthmatic attack, the allergic factor is of greatest importance; 70 per cent of asthmatic children are hypersensitive. This percentage agrees with the observation of many authors; hence the necessity of studying the allergic causes, the identity of which is determined by personal history, clinical data and tests for allergy. Accordingly, the author maintains that

the ideal treatment should comprise two simultaneous or alternating procedures, that is, treatment of the constitutional state and treatment of the allergic manifestation.

The author enumerates briefly all the therapeutic measures which in his experience are most efficacious, mentioning beneficial results from arsenic, iodides, magnesium hyposulfate orally and intramuscularly in desensitization and detoxification, before treatment of the asthmatic state. DWYER, Kansas City, Mo.

THICKNESS OF SUBCUTANEOUS FAT AS A MEASURE OF THE NUTRITIONAL STATUS OF SCHOOL CHILDREN. A. RNOTSALAIMEN, Ztschr. f. Kinderh. **60**:648 (April 1) 1939.

The various methods of evaluating nutrition are unsatisfactory. Subjective evaluation as well as height and weight tables are inaccurate. Formulas also are inaccurate and impractical. After reviewing the studies of several authors regarding thickness of the subcutaneous fat as a measure of nutrition, the author states that he is the first to make similar studies in the Scandinavian countries. He describes the technic he used to measure the thickness of skin and subcutaneous tissue lifted in a fold on various parts of the body. Tables are presented and explained. The results agree closely with those of Viennese authors. The author intends to determine the practical significance of his results by future studies.

SIEMSEN, Chicago.

STATISTICAL AND MYCOLOGIC STUDIES OF DERMATOMYCOSES OBSERVED IN PEIPING. J. W. MU and T. J. KUROTCHKIN, Chinese M. J. **55**:201 (March) 1939.

Fungous infections of the hair and skin are commonly met with, constituting 16.3 per cent of the clinical conditions in the dermatologic outpatient department of Peiping Union Medical College Hospital. In thirteen years over 6,000 persons showed signs of fungous disease of the hair or skin. The diagnosis was proved in 2,531 instances by finding spores and mycelia under the microscope. Favus of the scalp was present in 110 persons, in 92 of whom the fungus was found when the hair was examined. Clinical signs of tinea of the body were evident in 1,273 persons, in 720 of whose cases the results of microscopic examination were positive. Tinea of the hands and feet was diagnosed in 3,024 cases; in 1,245 of these, examination of the tissues was done, and fungi were demonstrable in 526. Tinea of the nails was present in 113 cases.

The incidence among males is many times greater than among females. Favus of the scalp attacks children chiefly; it is never found before the age of 5 years or after that of 30. Tinea of the scalp is a disease of youth, usually encountered in children between 1 and 15 years of age, the age group from 6 to 10 years containing the largest number of patients. The youngest infant affected was 3 months old, and there were 5 patients under the age of 1 year.

Mycotic diseases of the body, hands, feet and nails had their greatest frequency between the ages of 16 and 30 years, with a very low incidence in childhood, while under the age of 5 years no tinea of the hands, feet or nails was encountered. Poverty has an influence in the production of favus, and both favus and tinea of the scalp are most commonly seen in the spring. NEFF, Kansas City, Mo.

## Miscellaneous

CHROMIUM POISONING IN INFANCY. J. F. SANDER and C. D. CAMP, Am. J. M. Sc. **198**:551 (Oct.) 1939.

Chromium poisoning was observed in an infant aged 14 months, due to ingestion of a paint containing a relatively insoluble chromium compound. There was no evidence of local gastrointestinal irritation, The symptoms were systemic and gave evidence of an effect on the nervous system. The most important

observations were convulsions, stupor, dilated pupils, negative neurologic findings and normal spinal fluid. Chromium was found in the urine and feces.

EMSKE, Omaha.

CLINICAL EXPERIENCE WITH SULFAPYRIDINE: A REPORT OF THIRTY-THREE CASES. W. A. MACCOLL, J. Pediat. **14**:277 (March) 1939.

Thirty-three children ranging in age from 1 week to 13 years were treated with sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine). The children treated were divided into three groups: (1) those with pneumococcic infections; (2) those with bronchopneumonia caused by the beta type of Streptococcus haemolyticus and the haemolytic type of Staphylococcus aureus, and (3) a miscellaneous group, in which the majority of the conditions present were caused by the latter organism. The greatest effect of the drug was found in the group with pneumococcic infections. The drug seemed to have a promising effect in the children with bronchopneumania and was found to be beneficial when other treatment had failed. The results of treatment with sulfapyridine in the miscellaneous group suggested that the drug may have had some effect, but further study is necessary. Sulfapyridine was found to be effective in smaller doses and in lower concentrations than sulfanilamide. The toxic effects of sulfapyridine indicated that the precautions employed in the use of sulfanilamide apply likewise to sulfapyridine. In almost every instance the administration of the drug was accompanied by a lowering of the temperature. This was so constant that an antipyretic effect was suggested.

RAUH, Cincinnati.

EFFECTS OF INGESTED LEAD ON THE ORGANISM: II. STUDIES ON THE DOG. M. K. HORWITT and G. R. COWGILL, J. Pharmacol. & Exper. Therap. **66**:289 (July) 1939.

Horwitt and Cowgill previously showed that lead below 100 mg. per kilogram of food had no detrimental effect on rats. Similar experiments were made on 12 puppies from three litters. After being weaned, the puppies were given lead up to 100 mg. per kilogram of food for six to seven months. Examinations were made of growth, of the hemoglobin content of the blood and of erythrocytes for stippling, and in some cases, roentgen examinations were made for lead deposits in bones. After six to seven months the animals were killed, and either the different organs or the body as a whole was examined for lead content. In brief, growth and the hemoglobin content of the blood were normal. Very minute quantities of lead were excreted in the urine and considerable amounts in the feces, and small amounts were retained, of which by far the largest part was retained in the carcass (the total animal less the viscera), with only minute amounts in the viscera. The bones contained considerable lead, although the roentgenograms gave no evidence of this. One dog showed only illness, viz., bloody diarrhea and severe colicky contractions, in the seventh month, and this animal's bone retained the largest amount of lead of the group, 230 mg. per kilogram of bone.

PILCHER, Cleveland.

STUDIES ON THE EXCRETION OF SULFANILAMIDE BY THE DIGESTIVE GLANDS. M. K. HORWITT and G. R. COWGILL, J. Pharmacol. & Exper. Therap. **66**:289 1939.

The studies were made on normal dogs. The dose per kilogram corresponded to the clinical dose. The drug was excreted in the bile, pancreatic and gastric juices, succus entericus and saliva. The quantities excreted were considered to be bacteriostatic except those in the intestinal juices; the quantities considered bactericidal were: bile, 8 to 10 mg. per hundred centimeters; pancreatic juice, 8 to 10.5 mg.; gastric juice, up to 50 mg. In the intestinal juice the excretion was minimal.

PILCHER, Cleveland.

THE ANALEPTIC POTENCY OF SYMPATHOMIMETIC AMINES. M. L. TAINTER, L. J. WHITSELL and J. M. DILLE, J. Pharmacol. & Exper. Therap. **67**:56 (Sept.) 1939.

The gist of this detailed study, in the authors' words, is as follows:

"The fact that some of these amines produced no shortening of the recovery time although, when the animal's reflexes returned, they showed violent excitation, indicates that there are other modes of stimulation than those which are evidenced by the speed of recovery from a hypnotic. It therefore appears that in any rigorous consideration of the activity of analeptic agents they must be considered not as stimulants of the central nervous system as a whole, but rather as agents acting on some special part of it, and that their selection for use as antagonists to depression should be predicated upon a consideration of the locus of the depressant action. With the depressant used in this study, the actions were located primarily below the cortical level. In general, the sympathomimetic amines do not appear to be effective stimulants of this part of the central nervous system."

It is worth noting that some years ago, in a study of the respiratory action of caffeine, Schmidt pointed out that at certain stages of respiratory depression caffeine was a stimulant and at other stages it was a depressant and that it was not possible to be certain of the stage of depression. The present study was made on white rats with chloral hydrate, avertin and barbiturates as the narcotizing agents and various amines (epinephrine, tyramine, benzedrine, synephrine, etc.), coramine, picrotoxin and caffeine as the analeptic or stimulating drugs.

PILCHER, Cleveland.

AN EXPERIENCE WITH SULFANILAMIDE. V. TRIPPUTI, Med. inf., Rome **10**:274 (Sept.) 1939.

A boy of 12 years who was being treated for a griplike infection with the usual therapeutic doses of sulfanilamide suddenly presented agranulocytosis (white blood cell count, 2,000, with granulocytes 10 per cent, lymphocytes 60 per cent and monocytes 20 per cent). The symptoms were asthenia, pain in the bones, intestinal colic, dryness of the lips, epistaxis and fever. Laboratory tests eliminated the possibility that the condition was typhoid or paratyphoid fever, tuberculosis or malta fever. The blood cultures were negative. The treatment consisted of repeated blood transfusions. The patient recovered in about forty days.

HIGGINS, Boston.

UNEXPECTED DEATH IN CHILDHOOD. C. DE LANGE, Maandschr. v. kindergeneesk. **9**:45 (Nov.) 1939.

From the clinical and postmortem records in 16 cases of unexpected death of children the author draws the following conclusions: Sudden death in perfect health in the strict sense of these words occurs seldom. The most frequent direct cause of unexpected death in a young infant is bronchitis or bronchopneumonia, often still in the initial stage. Sudden or unexpected death in status thymicolymphaticus (cardiothymicus) and in spasmophilia is caused by heart failure. The same probably holds true for sudden death in eczema infantum. Several circumstances must cooperate; the liability of the nervous system is of great importance. The round cell infiltrations in the heart muscle which may be found in status thymicolymphaticus and in sudden death in eczema are not an essential part of these states. Their origin lies in myodegeneration of the heart or in myocarditis, to which children with these conditions are liable on account of the frequent infection of the air passages and skin. Death caused by pressure from an enlarged thymus gland on the trachea or from anomalies of the internal secretion of the thymus and also the occurrence of stridor thymicus are most exceptional, provided one may be inclined to accept them at all. The so-called ecchymoses of Tardieu are not pathognomonic for death from asphyxia.

VAN CREVELD, Amsterdam, Netherlands.

# Society Transactions

## AMERICAN PEDIATRIC SOCIETY

HERBERT B. WILCOX, M.D., *President*

HUGH MCCULLOCH, M.D., *Secretary*

*Annual Meeting, Skytop, Pa., May 2-4, 1940*

*(Concluded from p. 460)*

### Third Session

*Friday Morning, May 3*

**A Defect in the Metabolism of Aromatic Amino Acids in Premature Infants: The Role of Vitamin C.** DR. S. Z. LEVINE, DR. H. H. GORDON (by invitation) and MISS E. MARPLES (by invitation), New York.

A hitherto undescribed aberration in the metabolism of aromatic amino acids has been demonstrated in premature infants fed diets relatively high in protein (5 Gm. or more per kilogram per day) in the form of cow's milk without supplements of vitamin C. This aberration is as a rule not spontaneously demonstrable in full term infants on comparable diets, but it may be artificially provoked in them by feeding them the aromatic amino acids d,l-phenylalanine and l-tyrosine.

The defect consists in an inability to decarboxylate aromatic amino acids beyond the organic acid stage, and it is manifested by the appearance in the urine of the intermediary products, p-hydroxyphenyllactic and p-hydroxyphenylpyruvic acids in large amounts. These substances have been identified chemically and spectroscopically, and the absence of other intermediary products has been established by appropriate tests. The defect can be eradicated promptly by administering vitamin C in adequate doses. Of a number of other agents thus far investigated, only d-isoascorbic acid and a crude liver extract with added thiamine and riboflavin (E-795, Lilly) have been found to exert an analogous, though far less striking, effect. These data suggest that the defect is an interrelated function of at least three factors: the maturity of the infant, the level of the protein intake and the state of saturation of the tissues with vitamin C.

These observations provide a new approach for studying the intermediary metabolism of aromatic amino acids in the human organism and demonstrate a hitherto unrecognized function of vitamin C in human nutrition.

**Studies of Amino Acids.** DR. ALFRED T. SHOHL, DR. KENNETH D. BLACKFAN and DR. HAROLD L. HIGGINS, Boston.

A mixture of crystalline amino acids which closely approximated the amino acid content of casein was prepared, and dextrose and sodium chloride were added in appropriate amounts. This solution was administered intravenously to 3 normal infants. The solution we have found most satisfactory for intravenous use contains 2.5 to 5.0 per cent amino acid mixture or casein hydrolysate, 7.5 to 10.0 per cent of dextrose and 0.45 per cent of sodium chloride. From 100 to 150 cc. of such a solution per pound of body weight in twenty-four hours, given at the rate of 40 to 60 cc. per hour, will yield 40 to 80 calories per pound. Nothing was

given by mouth. The effects of this preparation were compared with those of an enzymatic hydrolysate of casein which had previously been shown to comprise an adequate source of nitrogen for human nutrition. As judged by positive nitrogen balances for short periods, the crystalline amino acid mixture gave results indistinguishable from those obtained with the casein hydrolysate. It was concluded, therefore, that such preparations so administered are adequate as the sole source of nitrogen for human nutrition.

As was observed with the casein hydrolysate, the crystalline amino acid mixture elicited an increase in body temperature in about half the cases when administered in sufficient quantity to supply nutritional needs. Therefore it was concluded that the rise in temperature was not due to an impurity in the preparation previously used but to the amino acids themselves. With either preparation the increase in temperature, when present, disappeared during the administration or immediately following it.

Observations were made of the metabolic rate under basal conditions and following the oral and the intravenous administration of casein hydrolysate. The metabolic rate was increased about 30 per cent when the amino acids were given orally and about 125 per cent when they were given in the same amount intravenously. The specific dynamic action of the amino acids is so much greater when they are given intravenously than when they are given orally that the heat produced is sufficient to account for the increase in body temperature if the mechanism for the elimination of heat is impaired.

Infants who for one reason or another could not take food by mouth showed excellent responses to intravenously administered amino acid mixtures. When such infants were given saline solution of sodium chloride and dextrose solution alone, they showed losses of weight and negative nitrogen balances; with the addition of amino acids to the intravenous fluids, they showed both increases in weight and positive nitrogen balances.

### DISCUSSION OF PAPERS PRESENTED BY DRS. LEVINE AND GORDON AND MISS MARPLES AND DRS. SHOHL, BLACKFAN AND HIGGINS

DR. GEORGE M. GUEST, Cincinnati: I should like to ask Dr. Levine whether this defect appears in older infants with scurvy.

DR. HIGGINS, Boston: The rise in body temperature accompanying the marked increase in metabolic rate suggests certain physiologic possibilities.

In the case in which there was marked increase in metabolism there was also marked rise in temperature. In the case in which metabolism had not been elevated so much there was no fever.

Dr. Lusk explained the specific dynamic action of protein as due to certain amino acids or to the by-products of their catabolism; thus, aminoacetic acid, alanine and leucine caused an increase in metabolism whereas glutamic acid did not.

An increase in a baby's heat production of 100 per cent should not under ordinary conditions cause a rise of temperature; the baby should be able to eliminate heat to balance the increase in production; for a crying baby does not get a fever, although his metabolism is increased considerably over 100 per cent.

It appears that the increase in metabolism is higher following intravenous than following oral administration of amino acids because certain amino acids are in the blood stream in much higher concentrations. It also seems that the same products which caused the increase in metabolism may have acted also on the heat center of the brain to raise the body temperature.

In starvation and in undernutrition the body temperature tends to go down to 96 or 97 F. When a person is overfed, the temperature tends to be higher, as 98.6. The thought arises that the metabolism of the amino acids may be quantitatively related to the increase in body temperature following the taking of food and to the lowering of body temperature in undernutrition.

DR. LEVINE: In connection with what Dr. Higgins said, it is of interest that when individual amino acids were used in premature infants a specific dynamic action was obtained with glycine and not with tyrosine or phenylalanine. The difference in response may have been due to the fact that the doses of the aromatic amino acids were smaller, but there is also the possibility that the lack of specific dynamic action with the latter amino acids was related to the inability of premature infants to decarboxylate these acids completely, since there is some evidence which suggests that the heat developed in the specific dynamic action of protein arises during the stage of decarboxylation and not during that of deaminization.

I should like to ask Dr. Shohl whether any split products of amino acid metabolism were found in the urine of the babies he observed.

DR. WARREN M. COX JR., Evansville, Ind. (by invitation): Protein hydrolysates are ordinarily prepared in either of two ways: hydrolysis with acid or hydrolysis with enzyme. Acid hydrolysis destroys tryptophan, and the replacement of even this one amino acid, which is an essential amino acid, is quite an expensive procedure. The casein hydrolysate which both Drs. Farr and Shohl used in their studies was prepared by enzymic hydrolysis. Approximately a year was spent in determining the conditions which might best be used to produce the maximum amount of amino nitrogen in the hydrolysate. When this stage of the work was complete, a large amount of the hydrolysate was prepared in order that the material used for studies in various laboratories might be of uniform quality. Even though approximately a ton of the enzymic hydrolysate was prepared, only a relatively small amount of this initial preparation remains.

To make the digest, casein is mixed with pancreatin (purchased as a commercial product) or with ground fresh raw pancreas. Bacterial putrefaction is prevented by the addition of toluene and chloroform. The mixture is allowed to digest at the optimum $p_H$ and temperature for approximately ten to twelve days, until the amino nitrogen, as determined periodically, reaches a maximum. When this has been attained, the material is heated, filtered and decolorized, and finally spray dried to give a fine, almost white, dry powder.

After the powder was obtained, it was particularly important to know whether it was nutritionally as satisfactory for growth as the original casein. This might not be immediately evident from a consideration of nitrogen balance. For this purpose eight groups of rats were fed on four different protein levels—i. e., with 5, 10, 15 and 20 per cent of either casein or the casein hydrolysate as the sole source of nitrogen. At comparable levels of intake, the group receiving the casein hydrolysate gained more in weight than did the group receiving casein. When the number of grams of weight gained per gram of nitrogen ingested was calculated, it was noted that the rats receiving the casein hydrolysate gained significantly more than those receiving the casein. This observation has now been repeated on three groups of animals, so that it seems clear there is definitely a difference in avor of the hydrolysate.

The casein hydrolysate has also been fed to dogs made hypoproteinemic by the procedure of Weech and Goettsch. It was observed under their conditions of depletion and regeneration that the casein hydrolysate was as effective in the regeneration of serum protein as casein itself. More recently observations have been made which are difficult to interpret. Stimulated by the studies of Whipple on the regeneration of hemoglobin and serum protein by single amino acids, Dr. Kemmerer, in our laboratory, has observed preliminarily that under the conditions of hypoproteinemia induced by the Weech and Goettsch diet 1 Gm. of methionine fed daily results in an increase in serum protein. To date he has used four amino acids singly: phenylalanine, glycine, cystine and methionine. He has observed that only methionine causes this increase, for which there does not seem to be any adequate explanation at present.

DR. SHOHL: I should like to ask Dr. Levine how long he can observe the good effects of previous vitamin C therapy continuing; i. e., how long will the effects last?

DR. LEVINE: I cannot answer Dr. Guest's question since we have not yet had an opportunity to study a patient with scurvy.

With reference to Dr. Shohl's question, the excretion of aromatic organic acids in the urine of premature infants may be maintained for as long as two or even three months by withholding dietary vitamin C. We have not continued observations beyond this time, for obvious reasons. The single administration of l-ascorbic acid in a large dose—200 to 500 mg.—will abolish the excretion of these substances for variable periods in different infants, perhaps for as long as two or three weeks. The daily administration of vitamin C in small amounts—20 to 30 mg.—will prevent the spontaneous appearance of these substances in the urine of premature infants receiving diets of cow's milk.

DR. SHOHL: I asked that question so that I could answer Dr. Levine's question. He asked whether we had found any increase in split products in the urine following the administration of casein hydrolysate. As we reported last year, there is an increase in the unidentified nitrogen, which may include those materials for which we did not search. We analyzed only for urea, ammonia, creatinine and amino acids.

**The Problem of the Association of Rickets and Scurvy.** DR. RICHARD H. FOLLIS JR. (by invitation), MISS DEBORAH A. JACKSON (by invitation) and DR. EDWARDS A. PARK, Baltimore.

In 487 autopsies on children aged between 3 and 19 months rickets was found in 238, or 48.4 per cent, and scurvy in 57, or 11.7 per cent. Rickets can be recognized in the skeleton by histologic methods at an early stage. Scurvy, on the other hand, does not declare itself until vitamin C deficiency has reached an advanced stage. Advanced vitamin D deficiency, i. e., advanced rickets, was discovered in 78, or 16.0 per cent, of the children in question.

In 57 autopsies on children between 3 and 19 months of age, in whom the presence of scurvy was proved by histologic examination of the bones, rickets, demonstrated in a similar way, was observed in 26, or 46 per cent. In all probability rickets was present in a greater percentage, because, when the scurvy was extreme, we could not always be sure that rickets was not masked by the scurvy.

We attempted to determine in living children the frequency of rickets in association with scurvy. The criteria used were a history of vitamin D deficiency and the season of the year when the infant came under observation, the results of clinical and of roentgen examination and the measurements of the calcium, inorganic phosphorus and phosphatase of the blood serum. The etiologic approach (the history of vitamin D therapy and the season of the year) proved practically useless. Clinical examination was found to be too gross a method to yield the fine distinctions necessary. The roentgen examination, also, proved too unrefined to reveal rickets unless this disease was well developed. The measurements of calcium and inorganic phosphorus in the blood serum also failed as a means of establishing with finality the presence of rickets. The difficulty here lay in interpretation. In all probability the threshold of inorganic phosphorus for the development of rickets varies in different infants and in the same infant at different times or under different conditions. We know that the threshold varies with age. We were unable to decide on a value which was decisive for rickets. We regarded 5 mg. per hundred cubic centimeters of blood or above as representing the normal and 4 mg. or below as indicating rickets in the majority of instances. In a considerable proportion of our cases the concentration of inorganic phosphorus lay between 4 and 5 mg. per hundred cubic centimeters. An estimation of phosphatase was made in only a few cases. The phosphatase levels in 2 cases showed variations so out of accord with the other criteria as to create doubt in regard to the value of the phosphatase level for the recognition of rickets. All the criteria in question gave only indirect evidence concerning the presence or absence of rickets. In some instances the criteria were contradictory; in other instances, however, one

or another of the criteria established the diagnosis of rickets beyond the possibility of doubt. We were able to prove the presence of rickets in addition to scurvy in only 5, or 17 per cent, of the 39 children studied.

The chief value of our clinical studies lies in the demonstration of the difficulties of recognizing rickets in the living child in the presence of scurvy, because of the inadequacy of the methods available. Undoubtedly, rickets was present in a higher percentage of instances than our data showed.

Is it not possible that an antagonism between vitamin C and vitamin D exists in the sense that a deficiency in the one vitamin may prevent a deficiency in the other from declaring itself in characteristic lesions, signs and symptoms. A deficiency of vitamin D results in failure of lime salts to be deposited in growing bone and cartilage. If the deficiency is severe and prolonged, the lattice of the calcified cartilaginous matrix framework, which is so characteristic of uncomplicated scurvy, does not form at all or else forms incompletely. On the formation of the scorbutic lattice, much that is characteristic of scurvy clinically, roentgenologically and histologically depends. It is the brittle scorbutic lattice framework which fractures. These fractures are most characteristic histologically. Moreover, the fractures of the lattice cause the characteristic extravasations of fibrin and sometimes hemorrhage which give the histologist such security in his pronouncement of scurvy at the cartilage-shaft junction. Moreover, the fractures of the lattice are accompanied by exudations of serum and appear to stimulate proliferations of osteoblasts in the intertrabecular spaces. These proliferations of osteoblastic cells constitute one of the most characteristic features of scurvy. The giving way of the lattice causes the cortex to break, the blood vessels of the periosteum to be torn, and blood to leak under the periosteum. If the deficiency of vitamin C is extreme and advanced, the signs can be recognized histologically even in the presence of extreme rickets. The most characteristic sign then lies in the connective tissue formations carpeting the spaces between the trabeculae. But in rickets, too, the formation of fibrous tissue in the intertrabecular spaces in the end region of the shaft is common and not always easy to differentiate from that of scurvy. Thus from the histologic point of view vitamin D deficiency certainly inhibits vitamin C deficiency from expressing itself and probably on occasion may mask vitamin C deficiency altogether. In the roentgen film rickets may prevent all the characteristic signs of scurvy, namely, the bright band at the end of the shaft (the lattice), the characteristic clefts and zones of rarefaction in and beneath the lattice and the shadows cast by the periosteum elevated as the result of hemorrhage. It may thus remove completely those evidences of scurvy in the roentgen film by which this disease is recognized. Clinically also, rickets interferes seriously with the recognition of scurvy. Both diseases give rise to enlargements of the costochondral junctions. Rickets may give rise to pain through fracture. If the lattice is not present to break, epiphysial separation does not take place, and so on. Quite probably, rickets prevents, to some extent at least, the development of the pain and tenderness that are characteristic of scurvy.

Deficiency in vitamin C, theoretically at least, should interfere with the development of signs of rickets. Osteoblastic activity is inhibited, and the development of the osteoid coverings of the bones, which is one of the cardinal signs of rickets, is diminished or stopped. However, our studies have shown that osteoid formation can be extremely well developed even in the presence of scurvy. Some of the roentgen changes produced by the two diseases are the same—for example, the cupping of the ends of the bones. As just pointed out, both diseases produce enlargements of the costochondral junctions. To use a slang expression, vitamin C deficiency "gums the game" when the latter consists in the diagnosis of rickets.

The question remains to be considered whether vitamin C deficiency prevents the development of the characteristic chemical alterations in the blood which are characteristic of rickets. A fairly extensive study carried out by us in order to elucidate this point failed because we used orange juice as the source of vitamin C. The orange juice not only healed the scurvy but started curative reactions against

the rickets and caused peculiar changes in the levels of the calcium and inorganic phosphorus in the serum, which made interpretations of the influence of vitamin C impossible.

**Influence of Hormonal Therapy on the Phosphatization of Rachitic Bones.** Dr. Henry J. Gerstenberger, Cleveland.

At the meeting of the society in 1938 I called attention to the fact that although parenteral administration of phosphoric acid solutions was able to bring about healing of rachitic metaphyses in monkeys, the continuation of this form of therapy did not prevent a second appearance of the rachitic condition of the metaphyses.

At that time it was also reported that parenteral administration of extracts of the parathyroid gland and of the anterior lobe of the pituitary gland had no healing effect on the rachitic metaphyses of light-deficient monkeys, while that of thyroxin did; however, it was noted that the effect of thyroxin was accompanied by a decided loss in weight and the development of a state of irritability, results which could not be accepted as being entirely satisfactory. In subsequent work, too, it was found that the healing influence of thyroxin in some animals gradually became less positive.

As a result of the observations just recorded, it was considered at least possible that in rickets or at least in advanced rickets a disturbance of some control mechanism is present and that this mechanism is concerned with the endocrine and the vegetative nervous system. In view of the progress that has been made in isolating from the anterior lobe of the pituitary body different substances, each with its own specific property, it was decided to check the results previously obtained with the gonadotropin in pregnancy urine by using instead a thyrotropic extract of the anterior lobe of the pituitary gland; in addition, an extract containing the gonadotropic and one containing the adrenotropic factor of this part of the pituitary gland were used. The studies with these two substances, however, have not progressed far enough to warrant the making of a report at this time; the same may be said of the status of the work so far done with an extract of the thymus gland.

Today's report, therefore, is limited to the presentation of results obtained with thyrotropic extracts of the anterior lobe of the pituitary gland.

Products from two different manufacturers were used simultaneously; the decision to do this proved to be of distinct value, as the product of one of the concerns possessed no potency or so little as to be negligible from the standpoint of demonstrating its effectiveness in the healing of rickets. Three rachitic monkeys which had for some time ceased to heal while receiving parenterally phosphoric acid solutions failed to show any response after the administration of solution 300, as this particular product was labeled, whereas those receiving solution 301, the product from the other manufacturer, showed decided healing. Evidence of healing began to appear approximately six weeks after the beginning of treatment with solution 301. The healing was not accompanied with a decided loss of weight and in some monkeys was accompanied with an increase in weight, and the animals did not become irritable. These observations suggest that this method of stimulating the thyroid gland is more probably the one that physiologically directs thyroid activity in normal bone formation.

Solution 301 was injected into 2 rachitic monkeys before any phosphoric acid solutions had been administered parenterally. One of these monkeys disclosed no healing effect even after a trial of ten weeks; when, however, parenteral administration of a phosphoric acid solution was begun, the healing response obtained was more outstanding than is usually experienced when the phosphoric acid solution is administered alone for the first time. Because of an uncontrollable development in the case of the second monkey, the experiences obtained in his case could not be used. (Lantern slides demonstrating roentgenograms and presenting figures on the chemical composition of the blood were used to illustrate the presentation.)

DISCUSSION OF PAPERS PRESENTED BY DR. FOLLIS, MISS JACKSON AND DR. PARK AND DR. GERSTENBERGER

DR. DANIEL C. DARROW, New Haven, Conn.: I should like to ask Dr. Park just why the scorbutic bone looks decalcified. What I have in mind is that it has always seemed to me that the rachitic bone was decalcified because the calcium and the phosphorus of the serum were low, and I thought that the scorbutic bone might look decalcified in the presence of normal levels of calcium and phosphorus. The answer to that question might clear up the confusion that has existed between rickets and scurvy from a roentgenologic point of view.

DR. ALFRED T. SHOHL, Mirror Lake, N. H.: I should like to ask Dr. Park if he would extend his discussion from the point of view of the occurrence of scurvy and rickets. His entire paper was limited to the discussion of the appearance of rickets and scurvy, and he has not discussed the other aspect of it.

DR. ALLAN M. BUTLER, Boston: I should like to ask two questions. First, I wonder whether in Dr. Park's large experience an appraisal of the mineralization of the bones by roentgen study has been any help in interpreting the values of the serum calcium and the serum inorganic phosphorus in rachitic patients. Perhaps I can clarify what I mean.

From the limited experience of some of us at the Children's Hospital, in Boston, it seems that if one looks at the mineralization of the bones as shown in the roentgen film, a lead is frequently obtained as to the significance of the concentrations of serum calcium and serum inorganic phosphorus. If you have minor demineralization of bone with some healing of the rickets, you may find serum calcium slightly lower than normal and serum inorganic phosphorus increased. If you have marked demineralization of bone with severe vitamin D deficiency, then with some healing you find both serum calcium and serum inorganic phosphorus low, the latter remaining low even in the presence of tetany.

In the second case in which rickets and scurvy were observed, our experience would suggest that the serum phosphatase rose following the administration of vitamin C. I therefore wonder whether the phosphatase rose after the administration of vitamin C and the healing of the acute scurvy.

DR. PARK, Baltimore: I wish to object to Dr. Kramer's remark that there was increased mineralization in the bones, provided he meant that increased mineralization was a primary condition.

Chemists tend to think of bone as if it were a mass of dead substance. They speak of the deposition of lime salts in bones and the removal of lime salts from bones as if the underlying process could occur in the test tube. The reason that the mineral content of the bone in the case reported was increased is that there had been an increase in the amount of organic tissue capable of holding lime salts. The disease process is one of living cells. These for one reason or another produce an excessive amount of organic material in which lime salts can be deposited. This excess of material produced by the cells is not destroyed as under normal conditions. Consequently, mineral material accumulates in excessive amounts, and the ash content of the bone is increased.

Dr. Kramer said that the chemical analyses of the bone showed increased calcium carbonate. Now, the child had rickets, and I should like to ask Dr. Kramer if the increased quantity of carbonate might not be explained on that ground.

The answer to Dr. Darrow's question, why the bones in scurvy look decalcified in the roentgenogram, is that there is an actual loss of substance in the bones. In rickets the new bone which is formed does not show. It is lacking in lime salts, so that it does not create any shadow in the roentgenogram. But in scurvy the bone is actually much reduced in amount. In other words, true rarefaction has taken place.

The common explanation of the rarefaction is that in scurvy osteoblastic activity is reduced, so that new bone forms not at all or to a very slight extent, and the physiologic destruction of bone which goes on all the time is unabated;

hence there is a continual loss of bone substance without any increase in bone substance. Probably in scurvy the destruction of bone is actually accelerated under the influence of vitamin C deficiency. At any rate, the reason why in scurvy the bones in the roentgen picture appear to be rarefied is that they actually are rarefied; in rickets the apparent rarefaction of the bone is a pseudo-effect; i. e., the bone is not nearly as much rarefied as it appears to be, but a large part of it, i. e., the bone formed under the rachitic influence, does not show.

In response to Dr. Shohl's question, our starting point in the clinical part of the investigation was scurvy. An attempt was made to determine the frequency with which rickets occurred in association with scurvy. We did not take rickets as a starting point and attempt to determine how often vitamin C deficiency occurred in conjunction with it. The latter project we have planned to undertake, and I think we could obtain an answer to the question of the association of scurvy with rickets in a much more simple way than an answer to the question of the association of rickets with scurvy, because Dr. Kajdi's test for vitamin C deficiency seems to be very accurate and gives the desired information directly. Unfortunately, there is no simple test for vitamin D deficiency, and the criteria on which we are obliged to rely for the establishment of rickets are indirect and too inexact to yield exact information.

I am not sure that I understand Dr. Butler's first question. I think that when Socrates asked his friends questions it would have been advisable for his friends to allow Socrates to answer them himself. I am afraid that I must suggest to Dr. Neff that he call on Dr. Butler and ask Dr. Butler to answer his own question, which I am sure he can do in a very wonderful fashion.

A series of slides which I failed to show had some bearing, perhaps, on Dr. Butler's second question. Dr. Kramer and Dr. Howland had the theory that vitamin C deficiency held vitamin D deficiency in check and that if a child having scurvy was treated with vitamin C the rickets would come out, so to speak. But, because we used orange juice, our results were interfered with to such an extent that we could not make any inferences from our work in this regard. In one case in which the child was treated for a number of weeks with ascorbic acid alone, there was a slight fall in the inorganic phosphorus with a progressive rise in the phosphatase, and in that case it did seem as if the rickets began to "come out." Perhaps the rickets was there all the time; perhaps it began with the administration of vitamin C.

We were quite prepared to think that when we treated the children with vitamin C the phosphatase would rise; i. e., we anticipated that if phosphatase is a measure of osteoblastic activity, the low phosphatase in scurvy would rise rapidly on treatment, so that it would reach a level such as one finds in rickets. Histologically, after treatment of scurvy with vitamin C, the bone, i. e., the growing parts of it, become literally alive with active cells. But, as nearly as we could determine from our data, such was not the case: If the phosphatase was low or normal to begin with, it did not rise under the influence of treatment with vitamin C.

**Neuroblastoma.** Dr. Sidney Farber (by invitation), Boston.

This communication is based on a study of 40 tumors diagnosed as sympathetic neuroblastoma which occurred among 301 malignant tumors studied at the Children's Hospital in Boston during the ten years ending Sept. 1, 1939. In each case the diagnosis was verified by biopsy or by postmortem examination. The term "neuroblastoma" ("neuroblastoma sympathicum" or "sympathicoblastoma") is used to denote the malignant member of the series of neoplasms arising from the sympathetic nervous system; the term "ganglioneuroma" describes the more differentiated and more benign member of this group.

The generalizations in this paper are based on the clinical experience of my colleagues Dr. K. D. Blackfan and Dr. W. E. Ladd and their associates and on the roentgenologic findings of Dr. G. A. Wyatt, as well as on the results of

studies which my associates and I have made concerning the structure, nature and course of each of these tumors. In agreement with recent opinions, our findings give no support for the perpetuation of terms such as "Hutchinson's type" or "Pepper's type" of neuroblastoma. The primary tumors arose in a variety of locations in addition to the adrenal medulla: paraganglionic tissue adjacent to the adrenal gland, the celiac plexus, the organ of Zuckerkandl near the bifurcation of the iliac arteries, the superior cervical ganglion, sympathetic tissue at the root of the lung with invasion and subsequent replacement of the lung, and retropleural and retroperitoneal locations, with invasion of the extradural space surrounding the spinal cord in some instances.

We have been forced to modify the almost hopeless prognosis given when neuroblastoma is discovered. Ten of the 40 patients in this series are alive from three to eight years after operative discovery of the tumor. The treatment varied from: (1) complete removal of the primary tumor with no subsequent irradiation of the site; (2) removal of a biopsy specimen from an inoperable tumor which had not metastasized, with no subsequent irradiation of the remaining tumor; (3) partial removal of a primary tumor which had not metastasized, followed by irradiation of the remainder; (4) removal of a primary tumor and biopsy of one of numerous metastases to the liver, followed by irradiation; (5) complete or incomplete removal of a tumor which was undergoing differentiation into a ganglioneuroma, with and without subsequent irradiation.

Three observations concerning the course and treatment of neuroblastoma may be permitted on the basis of this limited experience: (1) The tumor may undergo spontaneous hemorrhage and necrosis and disappear without any treatment other than biopsy; (2) it may undergo spontaneous maturation and become ganglioneuroma, which, as stated, is benign; (3) it may be treated successfully by radiation even after local metastasis has occurred. Radiation should prove a valuable and perhaps successful means of therapy after indicated surgical procedures have been carried out.

Two general statements which may be used as a guide for more successful treatment of neuroblastoma and other malignant neoplasms of early life are suggested:

1. Every solid tumor in early life should be considered malignant until proved otherwise by pathologic examination of the removed tumor.

2. Removal of the tumor should be effected without delay after a short period (twenty-four to forty-eight hours) of well organized diagnostic study and preoperative preparation; radiation therapy may be instituted subsequently.

DISCUSSION

DR. HENRY F. HELMHOLZ, Rochester, Minn.: All are indebted to the essayist for presenting a matter that has been a source of worry to all—a group of patients that are usually seen entirely too late to help.

I wish to ask about two things: Has Dr. Farber seen successful use of radiation in those cases in which the metastases were in the skull?

The other thing of interest is the percental incidence of these tumors. It may be due to the nature of the material at the Mayo Clinic that my colleagues and I see this type of tumor much less frequently than we do the so-called Wilms tumor. If I recall our statistics correctly, we probably see 1 tumor of this type to 4 or 5 of the Wilms type.

There is one other matter—that of immediate surgical removal. As Dr. Farber said, roentgen treatment gives excellent results in reducing the size of the tumor, and I just wondered whether immediate surgical removal is always indicated or whether roentgen treatment of the primary mass might not reduce somewhat the risks of immediate surgical operation.

DR. CHARLES G. KERLEY, New York: I am able to add 2 cases of neuroblastoma to the discussion. Both the patients were girls. One was operated on at the age of 9 weeks, by Dr. Meredith Campbell, of New York. The child is

now 5½ years of age and perfectly well, of the average height and development for her age. The other patient is a girl of 14 years. I had occasion to see her recently. She is strong, well and normal in all respects. The tumor was removed at the age of 2 years and 3 months, by Dr. John F. Erdmann, of New York. The right kidney was involved in both patients.

Dr. Farber, Boston: We have not yet been able to treat successfully metastases to the skull, but we have not had much opportunity so far. The only success we have had in the radiation treatment of neuroblastoma after metastasis has taken place was reported on the lantern slide: the 2 patients who had had metastases to the liver. The group at the Children's Hospital intends to use radiation treatment on every patient with metastasis anywhere in the body, including the skeleton.

Wilms' tumor (embryoma of the kidney) is the most common tumor in the renal region. Over the last ten years there were roughly 4 cases of neuroblastoma with the growths in all locations of the body, to 3 of Wilms' tumor each year. Had I taken the preceding ten years for analysis, Wilms' tumor would have been more common in our series.

Dr. Helmholz raises an important question concerning preoperative irradiation of neuroblastoma. With my clinical colleagues at the Children's Hospital, including Dr. Ladd and Dr. Blackfan and the members of the department of pathology, we have come to the conclusion, after a careful consideration of the entire problem, that the first step in the treatment of any solid mass in early life should be operative removal. After this step has been carried out, the question of radiation therapy is discussed. As I mentioned before, metastasis is no contraindication for radiation therapy. There are many reasons why this conclusion was reached. We have found that delay in removal of a tumor mass in early life is dangerous. It is clear that the exact time of metastasis or of direct spread into venous and lymphatic channels cannot be determined. The few weeks' delay occasioned by preoperative irradiation of the tumor may be long enough to permit dissemination of tumor cells either as a result of spontaneous activity of the tumor or of irradiation itself. We follow this rule in the treatment of all solid masses in early life. Unless incontrovertible evidence in favor of preoperative irradiation of the tumor is presented by other observers, we shall continue to advocate immediate removal of tumors in early life and subsequent radiation therapy, when indicated, as the best and most conservative method of treatment of tumors in infancy and childhood.

In response to Dr. Kerley's comments: I am delighted to hear that he has had 100 per cent success in the treatment of neuroblastoma in New York.

Dr. Frank C. Neff, Kansas City, Kan.: Dr. Farber, is it true in your experience that metastasis to the orbit originates from the left adrenal?

Dr. Farber: It may come from the right.

Dr. Charles G. Kerley, New York: Ours were both from the right.

**Progressive Myositis Ossificans (Progressive Ossifying Fascial Hyperplasia).** Dr. Donovan J. McCune, New York.

Progressive myositis ossificans is a genetic disorder of development which is characterized by metaplastic production of bone in the tendons, fascial boundaries and aponeuroses of the body and also along the course of the intermuscular and intramuscular connective tissue. In typical cases the hands and feet disclose dyschondroplastic changes leading to microdactyly and hallux valgus. The disease commences in childhood and is apt to remain active throughout the whole period of the normal development of the skeleton. Individual lesions commence with sudden metaplasia of the mesenchymal structures already mentioned: Following a period of preliminary swelling, sometimes accompanied by the appearance of cartilage, true bone is laid down. Clinically, the patient shows localized tender swellings which in the beginning are firm but not hard but which later assume

bony consistency as ossification takes place. The final result of the disease is the production of an elaborate system of extraskeletal bone which may completely immobilize the extremities and which leads to total incapacitation. The disease is sometimes confused with hereditary deforming chondrodysplasia and with interstitial calcinosis.

Two cases are reported. In the first the clinical features combined with histologic features that were misinterpreted led to an erroneous diagnosis of von Recklinghausen's neurofibromatosis. In the second case a similar misinterpretation caused the disease to be regarded as sarcoma with origin in soft tissues. In the second case survival was for a time attributed to roentgen therapy. One of the patients is now being treated with large doses of an estrogen with the intent of accelerating the maturation of the skeleton, in the hope of curtailing extension of the disease.

**Chemical and Histologic Study on Marble Bones, with a Case Report.**
DR. BENJAMIN KRAMER, DR. MAX LEDERER (by invitation), DR. BERNARD PINES (by invitation) and HENRY YUSKA (by invitation), Brooklyn.

Chemical examination of the bones in a case of juvenile osteopetrosis presented at a previous meeting of this society—which histologically were typical of osteopetrosis—revealed the following: (1) hypermineralization and (2) a residual calcium-phosphorus ratio corresponding to that of tertiary calcium phosphate and a value of N, i. e., the molecular ratio of tertiary calcium phosphate to calcium carbonate, of approximately 2. The normal value at the age period represented in this case is nearer 3, so that these bones seemed to be relatively rich in calcium carbonate. Since this also obtains in rickets there remained some doubt as to whether these findings were pathognomonic of osteopetrosis.

Another patient with juvenile osteopetrosis, 18 months old at the time of death, presented when first seen (1) retardation in both mental and physical development, (2) bilateral optic atrophy, (3) splenohepatomegaly, (4) characteristic roentgen evidence of osteopetrosis in both the long and the flat bones and (5) rickets.

This child was treated with large doses of vitamin D and ascorbic acid, and the bone lesions healed except for the osteopetrosis. The calcium, inorganic phosphorus and phosphatase concentrations of the blood serum returned to normal.

The newly formed bone presented uniform density with complete absence of trabeculation just as in marble bones. The anemia was uninfluenced by treatment except for temporary improvement following transfusion. Chemical examination of the bones bore out previous observations of the characteristic combination of hypermineralization with relatively high calcium carbonate content, the former explaining the dense appearance of the bones in the roentgen pictures, the latter accounting perhaps for their fragility. Histologic studies revealed changes in the provisional cartilage in the juxtaepiphysial region of the diaphysis, as well as in the diaphysis itself, and in the periosteum and the bone marrow. In general, the following abnormalities were present:

1. An irregularity in the size of the cartilage cells in the provisional zone and atrophy of the cells.
2. An inadequate preparation of the epiphysial cartilage for its role in endochondral bone formation.
3. A lack of primordial vascular channels invading the marrow.
4. A compensatory widening and sclerosis of the periosteal bone layer.

Other abnormalities included dense masses of calcified chondro-osteoid bone tissue in the juxtaepiphysial region and diaphysis, masses of lamellar bone, early membranous bone, primitive reticular bone trabeculae and changes in the bone marrow. Areas of diminished bone density running across the diaphysis of the long bones and as concentric rings in the bodies of the vertebrae were observed roentgenologically. Anatomically, the dense chondro-osteoid tissue was replaced by (1)

areas of massive hemorrhage and fragments of bone trabeculae in fibrous and cellular marrow and (2) areas of large interconnecting lamellar bone trabeculae with cellular marrow between. Further details will appear in the complete case report.

DISCUSSION OF PAPERS PRESENTED BY DR. MC CUNE AND DRS. KRAMER, LEDERER, PINES AND YUSKA

DR. L. EMMETT HOLT JR., Baltimore: At least one factor in the genesis of this complicated disturbance of ossification seems to be a failure of the disintegration of the calcified cartilaginous matrix. The forces which normally produce this disintegration are not known. Efforts to explain it on the basis of local factors which affect the solubility of calcium salts have not been successful. It is possible that the difficulty resides in the enzymes which hydrolyze the chondroitin–sulfuric acid complex of the matrix. Such chondrosulfatases are known and have recently been studied by the Japanese investigators Soda and Egami (*J. Chem. Soc. Japan* **59**:1202, 1938). Their methods would seem to offer a new approach to the problem of marble bone disease.

DR. S. GRAHAM ROSS, Montreal, Canada: I should like to make one clinical observation in connection with this case of Dr. Kramer's.

During the past winter I saw the roentgen pictures of an 11 month old child, seen for the first time then. These showed the typical appearances of osteopetrosis with one exception, namely, that the process had apparently stopped and there was normal bone formation at the ends of the long bones. The radiologists, judging from the length of growth at the ends of the bones, stated that the process had probably stopped at birth.

DR. MCCUNE: The general laughter has answered Dr. Powers' question; the "roentgen lesions" are artefacts; the structures referred to are mechanical devices employed to mount the skeleton. I wish to ask Dr. Kramer whether or not evidence of hyperplasia or hyperfunction of a parathyroid body was detected in his case. A positive finding in a child with rickets would obviously be open to a question of interpretation; nonetheless I am curious, because there is one well known case recorded in the literature, that of Péhu and Policard, in which the parathyroid bodies were conspicuously enlarged and the renal pelves filled with calcified material. This evidence does not immediately suggest that Albers-Schönberg disease is due to hyperparathyroidism, but it does suggest the possibility that the parathyroid bodies may be stimulated to hyperplasia or hyperfunction in order to maintain humoral equilibrium in the presence of a skeleton which is so voracious of calcium.

DR. LASLO KAJDI, Baltimore (by invitation): I am only a guest here, but may I make a comment? In Baltimore my colleagues and I have studied 2 patients with myositis ossificans progressiva. Both were adults over 30 years of age; one was a man, the other a woman. The woman had two exacerbations of new bone formation during the period of observation; so it seems that not in every case does the disease come to a standstill at about the age of 26. I should like to emphasize the fact that frequently new lesions will be initiated when one removes any of these diseased bones.

We determined the phosphatase in the blood of these patients. To our surprise the phosphatase was low as determined by the Bodansky method, both in remission and during the formation of new, pathologic bone; in both cases it was about 1 unit. Therefore the question is raised whether an increase in phosphatase is due to new bone formation or to bone destruction.

Dr. Hamilton described a biologic test for the demonstration of increased parathyroid activity. Rabbits are used. This test gave negative results in both our cases.

DR. KRAMER: Dr. Pines' careful study of the dynamics and of the histologic appearance of this process certainly indicates an awareness of the importance of the biologic phases of the process.

With respect to the question of hypermineralization, the high percentage of minerals was determined in the dry, fat-free bone. Hence the increase in the proportion of mineral matter to organic matter was actual.

In our previous paper, describing the first case, we discussed the possibility that rickets offered an explanation for the excess of calcium carbonate. We were unable to reach a final decision because in the previous case there had been definite histologic evidence of active rickets. In this case, however, we had an opportunity to treat the patient and to observe her for months after the rachitic process was completely healed.

Therefore it seems rather doubtful that the chemical change could have been accounted for as due to rickets.

Dr. Ross has pointed out something which is very interesting. In studying the literature of various cases it is surprising to find that patients who apparently have received only the usual, or only incidental, antirachitic therapy fail nevertheless to show rachitic lesions. Some children show areas of alternate condensation and rarefaction at the ends of the bones, as if there had been periodic attempts at healing.

This would indicate that there may be variation in the severity of the rachitic lesions as well as in their sensitivity to antirachitic therapy and to dietary inadequacy. The sclerotic lesion may also vary in severity, distribution and extent.

With respect to the relation between this disease and the parathyroids, I can say that all the parathyroid tissue was carefully examined and no hyperplasia found. The Hamilton-Schwartz test was done several times to exclude the possibility of an increase in parathyroid hormone in the blood.

**Serum and Tissue Lipids in a Peculiar Type of Generalized Lipodystrophy (Lipohistiodiaresis).** Dr. Arild E. Hansen and Dr. Irvine McQuarrie, Minneapolis.

An unusual opportunity to study that phase of fat metabolism pertaining to the storage and utilization of depot fat occurred when a 4 year old boy with a complete loss of adipose tissue was admitted to the pediatric service of the University of Minnesota Hospital. In addition to the generalized lipodystrophy, the child was found to have marked cirrhosis of the liver, fibrosis of the spleen and pancreas and diabetes mellitus, the latter developing during his stay in the hospital.

Study of the serum lipids during fasting and after a high fat feeding disclosed that neutral fat was present and that apparently fat was absorbed into the blood stream in a normal manner. Determinations of the respiratory quotient under various conditions suggested that the child was able to burn fat as well as to synthesize it from carbohydrate. On the other hand, studies on autopsy specimens showed that the neutral fat fatty acids of the blood serum were greatly diminished. Analyses of the pancreas, kidney, muscle, brain, liver, adrenals, spleen, skin, subcutaneous tissue and perirenal tissue for lipids disclosed a striking loss of neutral fat fatty acids from these various tissues. Comparison of the values for tissue lipids in this case with the values in a case of subacute nephritis disclosed that this loss of neutral fat was particularly marked in the skin and in the perirenal tissue and to a lesser extent in the liver.

The problem therefore seemed to be that neutral fat, after being absorbed into the blood stream, was not deposited in the tissues. No histologic abnormalities were found in the endocrine glands other than the fibrosis, and a decrease in islet tissue in the pancreas, and neither the clinical picture nor the chemical findings in this case seemed to correspond to those present in any of the known experimentally produced endocrine disturbances in laboratory animals. Although both the pancreas and the adrenals influence the deposition of neutral fat in the liver, as do also such substances as choline and betaine, nevertheless the physiologic effects of these factors are not said to produce changes similar to those found in this peculiar type of lipodystrophy.

The chronic fibrosis of the liver and of the pancreas in this case makes it difficult to deny that the cirrhotic changes in these organs may not have been fundamentally related to the disturbed metabolism. However, in the light of present knowledge we do not feel justified in explaining the findings on the basis of these factors alone or on the basis of a disturbance of the endocrine glands, of neurogenic function or of enzyme activity. In view of the fact that this syndrome does not seem to fit into any described symptom complex, the name "lipohistiodiaresis," or possibly "alipogenesis," is suggested to describe this failure of body fat to be deposited. Knowledge of the nature of this disturbance when interpreted in the light of future findings in the broader field of lipid metabolism may be of considerable value in leading to more complete comprehension of at least that phase of lipid metabolism which deals with the deposition and utilization of neutral fat.

DISCUSSION

DR. ALLAN M. BUTLER, Boston: I do not forget the attitude of the Greeks toward Socrates and the annoyance he caused them. Nor am I unmindful of his fate. However, I wish, very meekly, to ask a simple question. What was the blood pressure of this patient?

DR. HANSEN: In reply to Dr. Butler's question, the blood pressure, determined at numerous intervals, was always within the normal limits.

## Fourth Session

*Friday Evening, May 3*

**Antipertussis Immune Serum: Titration of Its Protective Power in Mice.**

DR. WILLIAM L. BRADFORD, DR. CHRIS P. KATSAMPES (by invitation) and DR. HENRY SCHERP (by invitation), Rochester, N. Y.

By intranasal inoculation of 0.05 cc. of a standard suspension of a culture of freshly isolated Haemophilus pertussis, an infection is regularly produced in mice. The protective power of antipertussis serum may be determined against this infection.

Hyperimmune human serum, immune rabbit serum and a globulin fraction prepared from it all protected the test animals to significant degrees.

One hyperimmune human serum with an agglutination titer of 1:1,280 possessed approximately four times as much protective power as did a similarly prepared serum with no agglutinins. A pooled rabbit immune serum with an agglutination titer of 1:20,000 protected against twelve and five-tenths times as many minimal lethal doses as it did after absorption had reduced its agglutination titer to 1 to 40. Another immune rabbit serum and the globulin fraction prepared from it by precipitation with sodium sulfate each possessed an agglutination titer of 1:2,560 and protected mice against 32 and 16 minimal lethal doses of organisms, respectively.

While the protective power of a serum may not be correlated with its agglutination titer, the experiments described suggest that a serum with a significant agglutination titer may be expected to possess a significant protection titer and that one with no agglutinins or a low titer of agglutinins may or may not be protective.

The highest mortality from pertussis occurs in infants under 6 months of age. Active immunization during this period of life is not effective because there is insufficient time for it and because the young infant does not respond well to antigenic stimulation. For this reason the potentialities of passive immunization have been studied.

Results obtained by testing the protective powers of various types of serum against experimental murine pertussis are described. It is proved that hyper-

immune human serum, immune rabbit serum and a globulin fraction prepared from immune rabbit serum, all possessed significant degrees of protection against the experimental mouse disease.

It is also shown that certain of these serums exert a favorable effect on the humoral antibodies and the clinical course of pertussis in infants. The relationship of this protection to the humoral antibodies is discussed.

DISCUSSION

DR. SCHERP, Rochester, N. Y.: It seems reasonable to expect that the technic for producing a true infection of mice by means of Haemophilus pertussis has provided a most important tool for the elucidation of the antigenic structure of this organism, especially, it is hoped, in relation to the human infection.

The aim of such a study of antigenic structure is twofold: (1) to improve the means of active immunization, and, as Dr. Bradford has suggested, (2) to improve immune serum for use in passive immunization and in the treatment of pertussis in the very young.

From a practical point of view the use of a concentrated globulin fraction may be important, assuming that the antibodies in the serum prove to be of value. It is possible to eliminate the majority of the native proteins with little loss of antibody, and by using the technic of desiccation from the frozen state one can achieve a final concentration of volume of about sixfold, which should simplify administration of the antibody.

It is of considerable interest, also, that with this organism there does not seem to be of any close correlation between the agglutination titer and the protection value of an immune serum. In addition to the data presented by Dr. Bradford, there are some recent results obtained with two old laboratory strains of Haemophilus pertussis, which had apparently lost a dominant surface antigen, for they were no longer agglutinated to a high titer by immune serum prepared against one of the strains shortly after its primary isolation. Nevertheless, the virulence of these strains for mice was not significantly diminished. This is a rather peculiar state of affairs with bacteria, and its meaning has not been exactly determined. Usually the loss of a surface antigen is correlated with a considerable loss of virulence.

**Virus Infection and Virus Immunization Studied by Use of Chick Chorioallantoic Membranes.** DR. RUSSELL J. BLATTNER (by invitation) and DR. JEAN V. COOKE, St. Louis.

The present paper is concerned with what we believe is a considerable technical improvement in the study of lesions caused by virus infection of the chick embryo. It is also concerned with some observations made by using the technic in the study of immune St. Louis encephalitis serum.

There have been difficulties in the recognition of foci of virus infection on egg membranes, since such foci must reach a certain size to be visible. These difficulties prompted an attempt to stain the cells of the infected foci to make them more readily visible. It was found that this could be done by vital staining of the membrane with trypan blue.

The method employed consists in spraying a small amount of a 0.5 per cent suspension of trypan blue directly on the membrane through a window in the shell when the egg is ready for examination. The dye is applied with an atomizer. The shell is closed and the egg incubated for from ten to thirty minutes. The membrane is then removed in the usual manner and washed gently in physiologic solution of sodium chloride to remove the excess of trypan blue; it is then fixed flat in a 10 per cent concentration of solution of formaldehyde U. S. P. for a few minutes. It is mounted in glycerin gelatin, covered with a cover slip and later sealed with Duco cement. This makes a permanent preparation of the membrane, which may be studied with the microscope. Even microscopic foci of proliferation in the lesions take up the trypan blue and are readily recognized.

The study of antivirus serum by means of egg membranes has been carried on chiefly by the use of serum-virus "neutral" mixtures, added directly to the chorioallantois. The method has been moderately satisfactory for certain viruses, but small foci of infection are difficult to recognize. We found that in the study of the virus of St. Louis encephalitis the trypan blue technic facilitates the demonstration of such neutralization of the virus by immune rabbit serum. The egg protection test produces results quite similar to those obtained with the mouse protection test, but mixtures not infective for mice still may contain sufficient free virus to produce foci of infection on egg membranes.

Another possible method of testing for specific antibodies on which we made some observations with the trypan blue stain is that of passive protection. It is a common observation that when a specific immune serum is brought in contact with cells they become protected from infection by the corresponding virus. This seemed applicable to chick membranes. In order to distribute the immune serum to all the exposed chorioallantoic cells, a small quantity (0.05 cc.) was sprayed on them with an atomizer and the virus inoculated twelve to twenty-four hours later.

Our results have demonstrated that by this method of passive immunization of egg membranes one can readily demonstrate specific antibody in antiencephalitis rabbit serum and also variola antibodies in the serum of patients convalescent from smallpox. We hope later to be able to make practical diagnostic observations on the serum of persons convalescent from encephalitis and to apply the test in other virus infections.

**Virus of Measles Grown in Developing Chick Embryo.** Dr. Gerald C. O'Neil (by invitation), Dr. Joseph Stokes Jr., Dr. Morris F. Shaffer (by invitation) and Dr. Geoffrey Rake (by invitation), Philadelphia.

The virus of measles can be carried on the chorioallantoic membrane of the developing chick embryo.

Such passage virus produced in monkeys a mild disease indistinguishable except, perhaps, in point of severity from measles produced in this animal with fresh virus from human patients.

Such passage virus produced modified measles of a very mild type in some children when administered by the intranasal or the subcutaneous route; in other children it produced mild respiratory symptoms or no symptoms.

Reinoculation of such children two to eight months later with nasal washings or blood from patients with measles in the prodromal stages or in the early stages of the rash produced no symptoms or signs, although monkeys and even, in one test, children used to control the activity of the inoculum had typical measles. In 2 children reinoculation with human blood was carried out five weeks after the inoculation of egg passage virus; one child exhibited mild measles; the other remained free of all symptoms but exhibited fever and a faint rash on the trunk, both of which would have been missed unless specifically looked for.

In corroboration of the older reports of Hektoen and other investigators, it may be said that measles can be produced in unvaccinated children by subcutaneous or intramuscular inoculation of blood from human patients, though the blood contains no demonstrable bacteria. Measles produced in this way was not modified in our hands.

### DISCUSSION OF PAPERS PRESENTED BY DRS. BLATTNER AND COOKE AND DRS. O'NEIL, STOKES, SHAFFER AND RAKE

Dr. Mitchell I. Rubin, Philadelphia: May I ask Dr. Cooke what was the interval of time between the instillation of the antiserum and the subsequent injection of the virus on the egg? I wonder if the interval was sufficient to

allow of development of cellular immunity. Or was there neutralization of the virus before the cells could be attacked?

Dr. William L. Bradford, Rochester, N. Y.: It will be of interest to test the durability of this artificially conferred immunity to measles. There is evidence that an attack of measles modified by administration of convalescent serum or of adult immune blood does not always protect against a later attack of measles. I have observed 2 instances of such failure.

From observation I can state that measles was accidentally induced by intradermal inoculation of a susceptible child with a mild amount of a bacterially sterile filtrate of throat washings. This type of inoculation might lend itself for trial by Dr. Stokes and his group working with the egg-virus material.

Dr. Blattner: Dr. Cooke asked me to close the discussion, Dr. Wilcox.

Dr. Rubin, in reply to your question, the immune serum in the passive protection test was sprayed on the membrane twenty-four hours before the virus was inoculated.

We are optimistic that the egg protection test, particularly the passive transfer technic, might be useful as a clinical aid in differentiating various types of encephalitis. The method is relatively simple, objective, and perhaps more sensitive than the mouse protection test.

This work is done in preparation for further, more important studies on clinical encephalitis, particularly the St. Louis type.

We also plan to use this method to sample the population for the presence of protective antibodies for these various diseases, both between epidemics and during epidemics.

Dr. Edward B. Shaw, San Francisco: I should like to inquire whether Dr. Stokes has determined the protective value of serum from these patients with modified measles, with the suggestion that thereby he might be able to determine the persistence of immunity in these patients. It has been my experience that modified measles does not necessarily give persistent immunity. Do these patients have persistent immune substances in their blood?

Dr. Stokes Jr.: Concerning Dr. Bradford's question, I am interested in that he inadvertently injected virus intradermally. Inoculations into the skin should be studied, since the lesion of measles certainly is in the skin, probably chiefly in the skin, or in the mucous membranes of the respiratory tract, and immunity probably would develop best from inoculation into the area which is most commonly affected by the virus.

As far as Dr. Shaw's question is concerned, we have collected serum from a number of the patients. There have been so many other tests that have been necessary on monkeys that we have not been able to carry out neutralization or passive immunization studies as yet, but we shall later.

**Bactericidal Irradiation of Air Breathed by Selected Aggregations.** Dr. W. F. Wells (by invitation) and Dr. Joseph Stokes Jr., Philadelphia.

The evaporation of minute droplets expelled in expiratory processes enables bacteria to ride the droplet nuclei on air currents. The confinement of air within human habitations during the winter season provides for concentration of these nuclei in the air people breathe. The aggregation of susceptible persons within the same enclosed atmosphere provides that proximity in time and space which characterizes the spread of contagion. Thus the conditions for spread of nuclei through confined atmospheres as indicated by sanitary analyses of air are identical with those for epidemic spread of manifest childhood contagion. A similarity of the pattern of spread of latent respiratory infection to clinically manifest contagion has been shown by immunity and sensitivity tests and by epidemiologic studies of age incidence. Though many factors complicate the clinical pattern of spread of air-borne infection, there is no reason to believe that the epidemic

pattern of the spread of infection differs from that simple basic pattern of spread of the clinically manifest contagion. Thus air-borne infection becomes contagious infection.

The staffs of the laboratories for the study of air-borne infection in collaboration with members of the department of pediatrics of the University of Pennsylvania School of Medicine have been studying, during the past three years, air disinfection as a means of cutting the lines of communication of infection, testing the hypothesis that air is a vehicle of contagion. Environmental control of respiratory infection in general and epidemic contagion in schools in particular has been attempted by ultraviolet irradiation of enclosed atmospheres. The following measures have been applied, either separately or in combination: direct irradiation of rooms where exposure can be limited by time or disciplinary protective devices; individual enclosures with bactericidal barriers to isolate stationary subjects, and indirect irradiation of enclosed space without direct irradiation of freely moving subjects. The irradiation of recirculated air provides a special case.

The direct irradiation of operating rooms to render the air aseptic furnishes a good example of the first principle. The second principle in its simplest form is illustrated by Dr. C. F. McKhann's barrier of the corridor, first tested in the Isolation Unit of the Children's Hospital in Boston. Extensions of this principle to barrier separation of cubicles from the corridor and from each other have been worked out at the Henry Phipps Institute, in Philadelphia, and first applied to the Cradle, at Evanston, Ill. At the Children's Hospitals in Boston and Philadelphia adaptations to the open-top cubicle have been made by creating an ultraviolet ray ceiling over the cubicle continuous with a curtain dropped in front of the cubicle. The elimination of 99.9 per cent of the test organisms liberated in one cubicle before they could pass by air currents into another cubicle has been demonstrated by tests at the Cradle. The elimination of more than 90 per cent of air-borne acid-forming organisms, indicating nasopharyngeal contamination, has been demonstrated in the irradiated ward of the Children's Hospital in Philadelphia.

In the Germantown Friends School, near Philadelphia, and in the ward for senile patients at the State Hospital in Marlboro, Mass., indirect irradiation through low slung central fixtures, without direct irradiation of the occupants, has accomplished the disinfection of test organisms at an average rate equaling the rate of elimination with a hundred air changes per hour. At Marlboro, reflecting ceilings increased the efficiency of indirect irradiation to a removal rate equal to that obtained by a thousand overturns per hour.

**Epidemiologic Study of Selected Aggregations Breathing Irradiated Air.**
Dr. Mildred Weeks Wells (by invitation) and Dr. Theodore Stanley Wilder (by invitation), Philadelphia.

Two types of congregations, continuous and intermittent, are under study by the staff of the laboratories for the study of air-borne infection as to the protection afforded the members against air-borne infection in general and contagion in particular by irradiation of the air with lethal ultraviolet rays.

The eight classes of the primary department of the Germantown Friends School represent intermittent aggregations. They have been under test for the past three years. The 170 children, aged 6 to 9, congregate for five to six hours a day.

The current year was marked by repeated exposure of the children in the irradiated rooms to chickenpox. Between December 8 and April 26 classes in which from 32 to 86 per cent of the members were susceptible were exposed eleven times. Secondary measles developed in 3 children (1 in each of three classes). For four days during the week of May 6, however, a child with unrecognized measles in the third grade (1 of the 3 children with secondary disease) daily exposed his own class and other children outside the irradiated atmosphere (in rehearsals for a class play). Between May 20 and 26, 14 children in the child's own class and 10 in other classes contracted the disease. This has been the only

epidemic spread of disease in the primary department during the three years and was definitely traceable to exposure outside the irradiated class rooms.

During each of the two previous years mumps spread epidemically in the unirradiated, but not in the irradiated, class rooms. In 1937-1938 one half only of the class rooms of the primary department were irradiated, the other half serving as a control. Mumps was introduced seven times into each group. In the irradiated class rooms 2 children, and in the unirradiated class rooms 12, acquired the infection. During the following year, 1938-1939, the entire primary department was irradiated. An epidemic of mumps occurred in the unirradiated intermediate department, with 27 children becoming infected, 16 in one class. In the irradiated primary department 2 introductions of measles resulted in secondary measles in 2 children.

Colds have not been controlled, and it is pointed out that so high a prevalence of any disease in the community that repeated exposure both within and without the school occurs makes the incidence of that disease a measure of susceptibility rather than of exposure within the school.

**Control of Air-Borne Infections in Hospitals.** Dr. Elizabeth Chant Robertson (by invitation), Toronto, Canada.

As a preliminary to remodeling a part of the infant ward, a room in the laboratory was converted into a small model ward; it was divided into cubicles by partitions and provided with an air-changing system. Tubular lamps emitting ultraviolet rays were mounted at the entrances to the cubicles. To test the efficiency of this arrangement harmless bacteria (Bacillus prodigiosus, which produces distinctive red colonies) were sprayed in one of the cubicles and then were caught and counted by the use of Wells's air centrifuge in the other cubicles. The air-borne spread of the bacteria was effectively prevented when the partitions ran from the ceiling to the roof, when the incoming air (maximum number of air changes, 10 per hour) was introduced near the floor at the back of the cubicle and removed near the ceiling at the front, and when six ultraviolet lamps were mounted around each entrance. Shorter partitions or fewer lamps allowed considerable air-borne spread. The ultraviolet ray lamps were sunk in boxes so that the radiation came out in a sheet across the front of the cubicle and did not extend back into the cubicle.

A special room, equipped as described but with, in addition, a separate hand basin near the entrance to each cubicle and with accommodations for 6 babies under 6 months of age, has been in use for the last five months. An ordinary room of the same size containing 6 cots was used as a control. The nursing and medical staff was the same for both rooms and was limited to the smallest number possible. Each member of this staff wore a mask and washed and applied a special bactericidal solution to the hands before handling a baby; in the ultraviolet ray room, glasses were worn.

A culture of material swabbed from the posterior pharyngeal wall was made in each case on admission when there was any evidence of fresh infection and routinely every week. Similar cultures were made of material taken from the staff every week and whenever respiratory infections developed. Group A hemolytic streptococci (the group pathogenic for man) and pneumococci were typed, also Bacillus influenzae and meningococci when these were isolated. Babies whose stay in the hospital was likely to be short were not admitted to the rooms. Thirty-eight babies have been treated in the special room and 36 in the control room. In the control room there occurred one outbreak of acute inflammation of the throat, with temperatures rising to between 100 and 102 F., in 3 of the 4 babies in the room at the time. Group A hemolytic streptococci were obtained from 2 of the babies and 1 nurse, but the strains were not of the same type.

There have been no cross infections in the special ultraviolet ray room. It has not been possible so far to show, by detailed examination of throat cultures, any evidence of transference of organisms from one baby to another in either room.

It is planned to carry on these tests for several years. There has been no evidence of any harm from the use of the ultraviolet ray.

### DISCUSSION OF PAPERS PRESENTED BY DRS. WELLS AND STOKES, DRS. WELLS AND WILDER AND DR. ROBERTSON

DR. FE DEL MUNDO, Boston (by invitation): My colleagues and I would like to show some slides illustrating the results of our work at the Infants' Hospital in Boston, in connection with bactericidal irradiation of the air.

The objects of our present studies have been, first, to find out if hospital infections occur now comparable with those which have occurred during the past three years; second, to make bacteriologic analyses of the air, and, third, to determine the effect of bactericidal irradiations on the incidence of cross infections and on the results of bacteriologic examinations of the air.

Our work at the Infants' Hospital started only last fall, and we tried to make as few changes as possible in the wards. We have limited our work to the Infants' Hospital for purposes of comparison with similar studies that have been carried on, and our main object has been to avoid the possibility of patient to patient contact.

The Infants' Hospital is divided into an upper and a lower ward, with a total of about forty beds. On each floor we have twenty beds, ten of which have lamps for ultraviolet irradiation of the surrounding air. The other ten are not provided with lamps, but the personnel are required to wear masks.

(Slide) This slide represents the ward without lamps.

(Slide) This slide represents the side with lamps. All the beds are in cubicles. We have tried to make the setup as simple as possible. We have made hardly any changes in the ward, and all our studies have been clinical observations; there have been no artificial experiments.

(Slide) This is a close-up view of one of the cubicles. At the entrance of each cubicle are two lamps, each with an aluminum reflector. The children and the personnel are not guarded with glasses or masks or any protection except white cotton curtains behind each reflector. We have found no untoward effects either in the children or in the personnel.

(Slide) This represents the curve of the bacterial count of the air in the infants' ward, weekly samples being taken before and after the lamps were installed. We started our studies in the fall without ultraviolet ray lamps. About the middle of December we started the installation of lamps. The solid bars represent the nursery for premature infants. The room is air conditioned and is not equipped with lamps. The plain bars show the ward with lamps and the cross-hatched bars the ward without lamps.

It will be noticed that the nursery for premature infants always had a low bacterial count, while the other wards had almost similar high counts of about 160 to 240 colonies to 10 cubic feet (0.28 cubic meter) of air, collected in the manner described by the previous speaker. It will be noticed how after the ultraviolet ray lamps were installed the counts of the wards with lamps dropped almost 80 to 90 per cent.

We have shown here incidentally the nursery for premature infants, where the counts have been practically uniform, i. e., about 15 to 18 colonies to 10 cubic feet of air, and we should like to show what the effect of increased activity or increased number of personnel in this nursery has been.

On this day, which was a busy one, there were 3 nurses inside the room for premature infants, and the counts were quite high; also, on this day there were 6 patients, whereas ordinarily we have 4 patients. There were 2 very sick premature babies, and we observed a rather high bacterial count. On subsequent determinations the count went down.

(Slide) This shows the incidence of infections at the Infants' Hospital in 1939-1940. Before the installation of lamps, i. e., from October to December, we observed 80 patients, and we had an incidence of infections of 11.2 per cent.

After installation of the lamps, from December to April, we observed 107 patients with lamps and obtained a reduction in the incidence of infections to 1.8 per cent. In the side without lamps but with masks for the personnel, we observed 155 patients and an incidence of infections of 12.9 per cent.

It will probably be wondered why without masks and before lamps were installed we had a lower incidence of infections than in a similar group after lamps were used. Here it must be noted that the first group was observed from October to December and the second from December to April, when we usually see a greater incidence of infections.

(Slide) Here I show the incidence of hospital infections since installation of the lamps, as distributed in different months. In December among the 10 patients with lamps there were no infections, while among the fifteen without lamps there was 1 infection. In January among 36 patients with lamps there were no infections, and among 38 patients without lamps there were 4 infections. In February we had 22 patients with lamps, without any infections, and 41 without lamps, with 6 infections. In March we had 26 patients with lamps, with 2 infections, while, of the 38 patients without lamps, 6 had infections.

In April the 13 patients with lamps had no infections, while the 23 patients without lamps had 4 infections. Altogether, we had in the wards with lamps 107 patients, with an incidence of 2 infections, whereas in the wards without lamps we had 155 patients, with an incidence of 21 infections.

(Slide) Incidentally, we should like to present here the incidence of air contamination which we observed in January of this year. This (indicating) represents the floor plan of our lower ward. On this side we had ten cubicles where the personnel wore masks, and on this side we had ten cubicles where no masks were used but lamps had been installed. You will notice that there were 2 patients with influenzal meningitis in the former ward.

The first of these 2 patients was admitted on January 15; the second, two days later. In each instance cultures of the spinal fluid and of material from the ears and nasopharynx were positive for a virulent type of Haemophilus influenzae. One day after admission of patient 1 we isolated Haemophilus influenzae from the air on the side on which both patients were, and we obtained negative results on the side with lamps. Then patient 2 was transferred to the side with lamps. We were not able to isolate the organism from the irradiated wards even after transferring this patient to it. We did isolate the organism from the side without lamps even two days after both patients were removed. Subsequent examinations, however, gave negative results.

In conclusion, therefore, we can state that although we have only a very small number of cases, representing a total of approximately 300 patients, the data are significant. Since this number is small, we cannot be very enthusiastic about our results, but we can state that so far these results have been favorable and encouraging.

DR. ROBERTSON: There is just one thing that I forgot to say, and that is the reason why this type of control ward was used. My colleagues and I wanted to compare the incidence of infections under the ordinary conditions with the incidence under what we hoped would be the best conditions.

## Final Session

*Saturday Morning, May 4*

**A Follow-Up Study of Reactors to Tuberculin and Children Exposed to Tuberculosis Who Had Been Removed from Contact.** DR. J. A. JOHNSTON, Detroit.

Eight hundred and twenty-eight reactors to tuberculin were removed from contact with tuberculous persons and followed in boarding homes for varying periods up to twelve years. The reinfection type of disease was detected in

33 of these children, in 23 of whom it developed after contact with tuberculous persons was broken. Of these 23 reinfected children, 18 had a history of exposure in their own homes.

There have been 2 deaths from tuberculosis among the children studied, one from a miliary process in an infant aged 3 months and the other from miliary disease in a child aged 15 years. This mortality is interpreted as favoring the view that something has been accomplished by the system of follow-up and preventorium care.

Quantitative estimations of hypersensitiveness to tuberculin were made periodically throughout the study, with the following results: (1) there was a quantitative fluctuation, for the most part unexplained, with a general tendency toward decline; (2) in 26 patients reaction was lost to 0.1 mg. of old tuberculin, and in 12 patients, to 1.0 mg.; in all except 3 of the latter there was roentgen evidence of calcification.

Among 135 children who had been in contact with tuberculous persons and who failed to react on their first examination, no evidence of tuberculosis was found on roentgen examination.

Two findings, viz., the presence of calcium in those losing reactivity and the absence of evidence of tuberculosis in contacts who did not react to tuberculin, suggest that the tuberculin test is an adequate screen for patients with significant disease in this age range.

Certain observations made on factors relating to the nutrition of the growth period brought out: (1) the high protein requirement of the growing child; (2) a correlation between negative nitrogen balances and the failure of tuberculosis to heal; (3) the depressing effect on the retention of nitrogen and calcium of the phenomena of puberty in the girl; (4) the similar effect of a focal infection and of (5) abnormalities in the basal metabolic rate.

**Specificity of the Tuberculin Reaction.** Dr. Waldo E. Nelson (by invitation), Dr. M. L. Furcolow (by invitation) and Dr. Barbara A. Hewell (by invitation), Cincinnati.

Studies are being conducted in an attempt to define more clearly the limitations of the tuberculin test. During the course of these studies it has been noted that when fairly large doses of tuberculin were injected skin reactions were obtained in the majority of the infants and children. A similar observation was made also in graded testing with coccidioidin.

The skin reactions to concentrated solutions of tuberculin were materially different from those to dilute solutions. The former developed more rapidly, reached their maximum size earlier and disappeared more quickly, and the area of elevation was less firm and more spongy. In the reactions to the smaller doses central necrosis was occasionally noted; it was never observed in the reactions to the larger ones.

Another apparent difference between the response to a high and that to a low concentration was observed. When simultaneous injections of the smallest dose of tuberculin were made in the forearms, the mean diameter of the reactions was essentially twice as large as the diameter of the reaction to a single injection in the same child. This relationship has not been observed between single and duplicate injections of the more concentrated solutions.

A series of injections of tuberculin was also given to three groups of children comprising, respectively, (1) those known to have active tuberculosis, (2) those with healed or quiescent lesions or who were suspected of having tuberculosis and (3) those who had been in contact with tuberculous persons. All the children with presumably active tuberculosis had reactions at a dosage level at which only 18 per cent of the group with initial disease reacted. The reactions to the more concentrated solutions in children with presumably healed tuberculosis and in those who were in contact with tuberculous persons but who presented no

evidence of tuberculous involvement had the same general characteristics as did the reactions in children who were assumed to be healthy and free from tuberculosis.

No suggestion is made that the activity of tuberculous lesions can or cannot be correlated with the degree of reaction to tuberculin. However, it appears probable that when reactions occur only in response to the larger doses this cannot be interpreted as evidence of specific sensitivity to tuberculin. The practical value of this statement is evident when it is pointed out that at least part of the reactions to the fourth test dose, which approximates in strength the commonly used second dose of purified protein derivative, appear to be of the nonspecific type.

### DISCUSSION OF PAPERS PRESENTED BY DR. JOHNSTON AND DRS. NELSON, FURCOLOW AND HEWELL

DR. CLEMENT A. SMITH, Boston: May I ask Dr. Johnston what his material has led him to think is the proper number of roentgenograms to take of such children while they are being followed? I mean, given a child who reacts positively to tuberculin, how often should that child be examined roentgenologically during the years that follow, particularly if such examinations have been omitted, as they often have been, until puberty approaches; at what time would Dr. Johnston advise starting a program of perhaps annual roentgen examinations for such children?

DR. CHARLES HENDEE SMITH, New York: Dr. Johnston and Dr. Nelson have opened a good many problems—in the first place, the old controversy between exogenous and endogenous infection.

A few years ago I was a member of a committee which talked for about two months, two hours a session, with a session every week, going over all the evidence as to exogenous and endogenous infection and at the end we found ourselves just where we were at the beginning, namely, in two camps.

It seems to me that any one who studies the natural history of tuberculosis and the dissemination of the disease must feel that there are good reasons for the belief that the second infection type of tuberculosis may be endogenous.

Dr. Opie made various statements and published articles some years ago in which a good deal of the argument rested on the fact that primary lesions are often in one lung and reinfection in the other. This was used as evidence against endogenous infection. He seems to me to have entirely overlooked the fact that the seeding of tissues with tubercle bacilli is hematogenous, and therefore the chances are perfectly even that the reinfection would be in the opposite lung. So it seems to me his argument falls down.

The old discussion about skin tests versus roentgenograms in case finding brings up the question of whether or not the skin test is of any value. Certainly, many people have shown that the roentgen examination is not a good filter for finding infected children; there are a large number of children whose roentgenograms are negative who have strongly positive skin reactions.

I should like to ask some questions of Dr. Nelson. As I understand it, his tests were all done with purified protein derivative. This brings up the question of purified protein derivative versus old tuberculin. If it is possible to get 100 per cent positive reactions by increasing the dose of purified protein derivative, with 80 per cent positive reactions at one year, as shown by the slides, either one is dealing with an abnormally tuberculous population or one has used a test which is too sensitive. It is not possible to get anything like that percentage of positive reactions with old tuberculin.

I cannot help pointing out the danger of retesting positive reactors. Not infrequently a child who has strong allergy (if you call it that) for tuberculin has been known to have been harmed by retesting. My colleagues and I have had a number of focal reactions in lungs from giving children second doses of strong

tuberculin, usually by mistake. We have a fixed rule that no child who has had a definitely positive reaction shall be retested in our service, because it is possible to start a flare-up in the lung.

DR. BÉLA SCHICK, New York: In relation to the paper read by Dr. Johnston, I am repeating to a certain extent what Dr. Smith said that the question of reinfection from within or reinfection from without is difficult to decide. I have frequently quoted Dr. Ghon on it, who, in spite of studying tuberculosis for twenty-five years, could not make up his mind as to how the adult type of tuberculosis develops. He was more inclined to accept the idea of endogenous reinfection.

The paper read by Dr. Nelson deals with the question of the so-called pseudoreaction which, as I have frequently pointed out, occurs in nontuberculous children. I have warned about the possibility of making a wrong diagnosis of tuberculosis on the basis of large doses of tuberculin. It has been proved that if a child is absolutely free of tuberculous infection, old tuberculin is tolerated without reaction. Even 1 Gm. of such tuberculin does not produce a reaction.

I wish to remind you of the high sensitiveness of children with active tuberculosis to tuberculin. My associates and I have had frequent discussions with Dr. Smith about the dosage of tuberculin. We studied the extent of sensitiveness to tuberculin in Sea View Hospital, an institution for tuberculous children. The sensitiveness of these children to old tuberculin is so high that almost every child reacts to the intracutaneous injection of 0.1 cc. of a dilution of 1 : 60,000. Frequently the sensitiveness is much higher (to 0.1 cc. of a dilution of 1 : 100,000 and even a dilution of 1 : 1,000,000).

Therefore, I always warn my staff against using stronger concentrations of tuberculin in testing if they have to deal with a child who is clinically suspected of having tuberculosis. It has been well known for a long time that larger doses of tuberculin may produce focal reactions. Frequently enough, it will be found that the temperature rises. This rise may continue for several weeks. In roentgen films increased shadowing may become visible.

I wish to remind you of the sensitiveness of tuberculous patients to deuteroalbumose and peptone and other substances. Papers are published to the effect that the tuberculous patient is sensitive even to his own serum.

If the stronger concentrations of tuberculin are used, pseudoreactions have to be considered. The latter disappear quicker than real reactions. Nontuberculous infants more frequently show pseudoreactions, as we so frequently use stronger concentrations for testing in order to rule out tuberculosis.

At present I see no particular advantage in using purified protein derivative.

DR. HENRY F. HELMHOLZ, Rochester, Minn.: My co-workers and I have also been interested in the problem of the relationship of reinfection or flare-up of the old infection to chronic ulcerative phthisis, and for some years Dr. Feldman and I have been studying the bacterial content of the primary Ghon tubercle and of the draining lymph glands. Much to our surprise, we have had negative results much more frequently than we had anticipated.

In children over 5 this would not be a surprise, but in children under 5 and even in those at the ages of 2 and 3 we have had negative findings on animal inoculation and also on culture, whereas we thought we would surely find viable tubercle bacilli.

Unfortunately, our series is still too small to enable us to draw any definite conclusions. Results so far make us feel that reinfection accounts for recurrence of tuberculosis more frequently than flare-up, although it must be admitted that there may be foci in which the tubercle bacilli continue viable, other than the primary Ghon tubercle and the draining lymph glands.

DR. JOHNSTON, Detroit: I will have to prepare another paper, I think.

I did not mean at all to leave the impression that it was believed that the endogenous was even the usual route. In any controversy like this, in which you get two extreme points of view, the answer is usually midway between.

Any extreme is a half-truth, and I should say that probably endogenous reinfection did not account for more than 5 to 10 per cent of the second infections.

In practice pediatricians all know the relatively greater importance of intimate contact with tuberculous persons over the flare-up. This was merely to demonstrate that within the limits of the setup it was possible to detect endogenous reinfection, and that it is worth watching for.

As to Dr. Smith's question about the number of roentgen examinations, if he will just look at that slide again, it will bring out one point, and that is this: Myers and his group would have one forget about the reactor until puberty is reached and then take a roentgen picture every year. Well, possibly that would have detected most of these; if one made a frequency curve, it would show a group around here (indicating)—about 11 to 15. But we did detect 2 cases at 9, 2 at 11, 2 at 12, 2 at 13, 4 at 14, 2 at 15, 2 at 17, and we are still following them. Thirty-six of the patients are now married, and 20 of them have children. I don't know what the age limit is for pediatrics any more, but these patients come back for roentgen examinations. One flare-up followed a third pregnancy.

Therefore I cannot give a categoric answer to that question. If funds were limited and one could take only a limited number, I suppose one ought to start taking them two years before the onset of puberty, because these metabolic changes become evident about then; also one should examine them when there is any intercurrent infection or when anything has occurred which has had an untoward effect on the total state.

As to the danger of tuberculin, I am glad that was pointed out. It is very real. We had a good many twinges of conscience about doing the repeated tests. On the other hand, it is a two-edged sword. Stuart Willis has shown some very interesting results from desensitization by using very minute doses in some rather hopeless cases, and all pediatricians know the beneficial effect of tuberculin on the phlyctenule. But I do not think it is generally appreciated how minute these desensitizing doses need to be. When we have any reason to suspect tuberculosis, we begin with 0.0000001 mg. and gradually work up to 0.000001, 0.00001 and 0.0001 mg. I am frank to say that I do not understand some of Dr. Nelson's results, since some of these children have been retested twice a year for twelve years, and in those whose reactions originally were negative the incidence of recurrent positive infection is very small.

I share Dr. Schick's feeling about purified protein derivative versus old tuberculin. We tried purified protein derivative the first year it was prepared, comparing it with tuberculin, in parallel series and found that the reactions to it were different. I mean, the wheal had a vague, noncircumscribed edge, and there were a number of cases in which we could not interpret it.

Again, we made daily readings for a while and found the peak of reactivity not at forty-eight but at about fifty-six to seventy-two hours, and a real reaction to tuberculin in a child with a positive roentgenogram will usually persist more or less indefinitely. The one I got from you, Dr. Powers, in New Haven, in 1923, lasted six months. I still have a scar.

I wonder about the interval of your testing, Dr. Nelson. I should like to know about that.

Dr. Helmholz, I am glad that you brought that work up. I mentioned it, at least the report on the adults that Feldman and Baggenstoss presented. I think that there are several criticisms of that, and they are best given by Max Pinner in his editorial "Endogenous Reinfection and Primary Complex," in the *American Review of Tuberculosis* (**38**:791-793 [Dec.] 1938), which you saw.

In the first place, the material was from patients who did not die of tuberculosis, and probably that is not fair. In the second, the possibility which Dr. Helmholz pointed out is real. The fact that one fails to grow organisms from a Ghon tubercle does not mean that there may not be a dozen other foci which might be the source.

Dr. Nelson, Cincinnati: In the first place I think I can say that we have no ax to grind for or against purified protein derivative. While we have not per-

formed a comparable series of tests with old tuberculin in which doses of the same magnitude were employed as in this series with purified protein derivative, the evidence which we have, some of which I presented before this group in 1937, points in the same direction for old tuberculin as it does for purified protein derivative.

I agree with those who mentioned the possible danger of large doses of tuberculin. This has also concerned us. I should have pointed out that in those cases in which we suspected tuberculosis we employed doses even lower than those mentioned by Dr. Johnston. The first test dose contained only 0.00000000001 mg. of purified protein derivative, which approaches an astronomic figure. Most of the children with active tuberculous lesions had skin reactions to 0.00000001 mg. of purified protein derivative.

I believe you had a question, Dr. Schick, as to the size of the dose. I have explained the precautions taken to guard against overdosage with tuberculin. Roughly we consider that a 1 : 10,000 dilution of old tuberculin is equal to 0.00002 mg. of purified protein derivative.

**Differential Bactericidal Effects of Various Urinary Antiseptics.** Dr. Henry F. Helmholz, Rochester, Minn.

This study comprises the differential bactericidal effects of the urine of patients given the ketogenic diet, mandelic acid, benzochrome, sulfathiazole (2-sulfanilamidothiazole) and sulfamethylthiazole (2-sulfanilamido-4-methylthiazole). From six to a dozen strains of the organisms found in urinary infections were used in this study—Streptococcus faecalis, Staphylococcus aureus and Escherichia coli, Aerobacter aerogenes, Proteus ammoniae and Pseudomonas of the gram-negative group. There was marked variability in the bactericidal action on members of the same group.

DISCUSSION

Dr. John D. Lyttle, New York: I should like to ask Dr. Helmholz whether he has any difficulty in obtaining the necessary concentrations of these drugs in the urine of patients with acute urinary infection.

Dr. Helmholz: It is quite remarkable that in sulfanilamide and sulfathiazole one probably has drugs that act better in kidneys with reduced function than any other of the urinary antiseptics, particularly the group that is dependent on urinary acidity.

It is almost impossible in patients with blood urea above 50 mg. per hundred cubic centimeters to get urine of $p_H$ 5.5 or below, and it is this range that is necessary in order to get a bactericidal effect with methenamine, mandelic acid or the ketogenic diet. Sulfanilamide has been of particular interest in the treatment of a boy who had a posterior urethral obstruction and who for some fourteen years now has had a urinary infection. My associates and I tried methenamine, the ketogenic diet and mandelic acid without ever getting sterile urine. On the other hand, with sulfanilamide in a concentration that never rose above 27 mg. per hundred cubic centimeters he had sterile urine for a period of about four days. There was a relapse, and thereafter we were unable to sterilize the urine with sulfanilamide.

I think that this group is particularly valuable in the treatment of patients who have lowered renal function.

**Storage of Vitamin A in the Liver and Its Liberation Under Various Conditions.** Dr. S. W. Clausen, Dr. A. B. McCoord (by invitation), Dr. W. S. Baum (by invitation) and Dr. J. O. Rydeen, Rochester, N. Y.

Young rats which had been reared on diets containing amounts of vitamin A just sufficient to cause normal growth were given single large doses of this vitamin. Groups of the rats were killed at intervals over a period of one hundred and fifteen days and analyses made of the tissues and of the gastrointestinal tract

for vitamin A. Under these conditions the vitamin A content of the liver remained constant for ten days and then fell at a rate approximately constant and proportional to the original dose. The decrease of vitamin A in the lungs and the adrenals began at once and followed curves which were nearly hyperbolas. If two days after receiving the large dose of vitamin the rats were inoculated with cultures of rat paratyphoid bacilli, the fall in the vitamin A content of the liver and lungs was more rapid than in the controls; whereas the vitamin A content of the adrenals rose. These observations indicate that infection may cause destruction, rapid utilization or rapid excretion of vitamin A and may cause liberation of this vitamin from stores. An attempt was therefore made to study the liberation of vitamin A from the liver into the blood. When dogs received large doses of methyl, ethyl or isopropyl alcohol by mouth, by superficial vein or by portal vein, a prompt, considerable, prolonged rise of vitamin A was observed in the blood but not in the lymph of the thoracic duct. This occurred even when the dogs had received no food for forty-eight hours. These observations indicate liberation of the vitamin from the stores. Repeated biopsies of the liver were made in 3 cases in which the dog received repeated doses of alcohol, and there was found a definite correlation between the concentration of vitamin A in the liver and the degree of rise of the vitamin in the blood. In those dogs with lower stores in the liver a marked decrease in these stores resulted from repeated injections of alcohol. The evidence points, therefore, to liberation of vitamin A from the liver by alcohol. During the experiments the stools and the urine contained very small amounts of vitamin A. The total amount of vitamin A disappearing from the liver was far in excess of the amount normally needed by the animal in the time of the experiment. It is not yet known whether this amount of vitamin was moved to other tissues or whether it actually disappeared.

**Vitamin A.** Dr. Charles D. May (by invitation) and Dr. John F. McCreary (by invitation), Boston.

During the past three years there have been developed a convenient method of estimating vitamin A in small quantities of blood which has been applied to the problems of early clinical diagnosis of vitamin A deficiency and to studies of the metabolism of vitamin A in health and in disease.

It has been learned that normal values for vitamin A in the blood cover a wide range but that in a given person the level is relatively constant throughout a day and from day to day.

Our investigations have revealed that there are a number of conditions in which the levels of vitamin A in the blood are altered far beyond the range of normal values. Particular attention has been given to the interrelationship between the intake of vitamin A and the level in the blood, especially as regards the detection of a deficiency of vitamin A.

It has been found that in normal infants and children the levels in the blood reflect the alterations in the intake of vitamin A. When the intake had been abundant before restriction of intake occurred, the levels in the blood did not drop below normal for several weeks. When the initial bodily stores were not large, reduction in the intake was followed relatively sooner by lowering of the levels in the blood.

The levels of vitamin A in the blood become very low before the appearance of the earliest clinical sign of deficiency of vitamin A, namely, cornified epithelial cells in the conjunctivas, the respiratory tract and the genitourinary tract.

By means of a vitamin A absorption test it was found that there was impairment of the absorption of this vitamin from the intestine in patients with atresia of the bile ducts, fibrosis of the pancreas and celiac disease. When these patients with impaired intestinal absorption ingested only ordinary amounts of vitamin A, their blood showed extremely low levels of the vitamin. If these low levels persisted, other clinical evidences of the deficiency of vitamin A appeared.

When absorption from the intestine is impaired, very large amounts of vitamin A must be given orally to maintain a normal level of vitamin A in the blood and to prevent the appearance of clinical evidence of the deficiency.

The level of vitamin A in the blood appears to be a useful direct clinical test for the early diagnosis of a deficiency of vitamin A. It is a useful means of determining the optimal daily intake of vitamin A and the circumstances under which the requirement should be increased.

**Vitamin A: A Comparison of Dark Adaptation Time and Serum Vitamin A Level.** Dr. Hugh W. Josephs, Baltimore.

In this work an attempt was made to learn to what extent the level of vitamin A in the blood and the sensitivity to dim light could be used to determine the presence of a deficiency of vitamin A. The subjects, about 180 in number and without significant illness, were divided into four groups on the basis of diet. Group 1 comprised children on diets containing adequate amounts of vitamin A; group 4, children whose diet and care were of the poorest. The adaptometer had been designed at the Johns Hopkins Hospital for viewing pictures first in a bright light and then in a dim light, the intensity of which was kept constant. Variations in adaptation were measured by the time taken to recognize certain details in the test pictures. The results were analyzed in a series of distribution curves.

With carotene it was found that there was a progressive shift toward lower values from group 1 to group 4; with vitamin A the shift, though definite, was less in the first three groups, and it was only in group 4 that it was sufficient to have diagnostic value. In other words, it was only when the diet was very bad and the maintenance on it prolonged that the serum vitamin A was sufficiently reduced in the majority of these subjects to permit conclusion that there was a dietary deficiency and that the low serum level of vitamin A was not due to some other factor. With regard to the adaptation time, the lack of shift in groups 2 and 3 and the pronounced shift in group 4 bring an analogous conclusion: that a moderate or even relatively severe dietary deficiency causes little if any shift in the expected values, and it is only in the severest deficiency that this deficiency can be shown to affect the adaptation time. In regard to both serum vitamin A and adaptation to dim light the spread in values is considerable, so that it is impossible to say that because a marked reduction in vitamin A or a marked disturbance in adaptation is presumptive evidence of deficiency, a milder reduction in vitamin A or a milder disturbance in adaptation is evidence of a milder deficiency. On comparing values for serum vitamin A and for adaptation time one finds little correlation over a considerable range, owing to the wide scattering of figures for both vitamin A and adaptation time; the only definite relationship was that most of the very low levels of serum vitamin A were associated with greatly prolonged adaptations.

DISCUSSION OF PAPERS PRESENTED BY DRS. CLAUSEN, MC COORD, BAUM AND RYDEEN, DRS. MAY AND MC CREARY AND DR. JOSEPHS

Dr. Daniel C. Darrow, New Haven, Conn.: What are the ages of the patients to whom this adaptation test can be applied?

Dr. Charles Hendee Smith, New York: May I point out that the instruments used by Hague and Lewis can be employed to test infants accurately?

Dr. Benjamin Kramer, Brooklyn: Was there any improvement in those subjects who showed the very low adaptation time when vitamin A was given, and, if so, how long did it take for that improvement to manifest itself?

Dr. Clausen: Dr. Baum and Dr. McCoord attempted to find a correlation between the vitamin A of the blood of patients and their adaptation to dim light as determined by the biophotometer. There was no apparent correlation except

in the few instances in which the vitamin A content was very low and the adaptation very poor.

Therefore, although the rough test with the biophotometer corresponded almost exactly with the tests that Dr. Jean has published, the results of which he interpreted as evidence of a deficiency of vitamin A, indicating deficiency in 25 per cent of the population, we certainly cannot confirm that high incidence from analyses of the blood.

DR. JOSEPHS: I applied the test in a study of one or two children as young as 4 years of age, but most of the subjects were over 5 years of age and mentally competent.

There were one or two questions. I don't know anything about lipochrome pigment in the fats. All I know is that the fats do not give positive results in tests for carotene, and I doubt if there is such an available store.

We did not give vitamin A to any patient who had delayed adaptation except in a single case, and the improvement was relatively slow. But I cannot answer that question.

**Treatment of Hypoprothrombinemia Haemorrhagica Neonatorum with Vitamin K.** DR. HENRY C. PONCHER (by invitation) and DR. KATSUJI KATO, Chicago.

In 20 cases of hemorrhagic disease of the newborn the prothrombin time was determined before and after the institution of treatment with vitamin K, for the purposes of diagnosis and prognosis, respectively.

The average time of onset of the hemorrhagic manifestations was fifty-four hours after birth; the latest was ninety-six hours, and the earliest twenty-four hours, after birth.

The frequency of the different clinical forms of bleeding was: hematemesis 15, melena 8, omphalorrhagia 7, dermal hemorrhage 3, cerebral bleeding (as indicated by symptoms) 3 and hematuria 1. In the majority of cases, two or more of these symptoms occurred in the same patient.

The distribution as to race and sex was: white babies 13, colored babies 7; boys 13, female 7.

Before treatment the average prothrombin clotting time giving a definite end point was two hundred and nine seconds; the shortest time was one hundred and ten and the longest two hundred and seventy-two seconds. In 11 cases the prothrombin time before treatment extended beyond five minutes.

The average prothrombin time for all cases during twenty-four hours after therapy was twenty-six seconds. In most of the cases the shortening of the prothrombin clotting time could be demonstrated within two to six hours after therapy.

The doses, routes of administration and preparations of vitamin K used in the present series were as follows: (*a*) 2 methyl-1, 4 naphthoquinone (Mead Johnson & Company), 10 mg. doses, oral administration; (*b*) 2 methyl-4 aminonaphthol hydrochloride (Parke, Davis & Co.), 1 mg. doses, intramuscular injections; (*c*) bisulfuric ester of 2 methyl-1,4 naphthoquinone (Abbott), equivalent of 2 mg., subcutaneous injection. While the water-soluble preparations can be effectively given intravenously, we chose the most accessible routes of administration for practical reasons.

With all preparations studied the clinical improvement was both prompt and permanent.

Blood transfusions were entirely avoided. Fluids were injected only in cases of dehydration.

The administration of vitamin K or its substitutes by oral, intramuscular and subcutaneous routes corrects the abnormal prothrombin clotting time of the blood which is characteristic of the hemorrhagic disease of the newborn. Since the acute manifestations of bleeding occur coincident with prolonged prothrombin clotting time, it is proposed that the prothrombin test be required for diagnosis

of this disease. Etiologically, the condition may best be designated as hypoprothrombinemia haemorrhagica neonatorum (Nygaard). Since vitamin K promptly reduces the prothrombin clotting time, its use in cases uncomplicated by severe posthemorrhagic anemia makes blood transfusions unnecessary. In the event of serious loss of weight or of evidence of pronounced dehydration, subcutaneous fluid may be injected. The microprothrombin test recently devised by Kato (1940) has been found admirably suited for diagnosis as well as for the following up of these cases.

DISCUSSION

DR. DONOVAN J. MCCUNE, New York: May I ask Dr. Kato to express an opinion concerning the routine use of vitamin K for prophylaxis?

DR. S. GRAHAM ROSS, Montreal, Canada: My colleagues and I have had, in the past winter, some experience with the estimation of prothrombin time in the newborn. We studied a series of 33 infants from birth until the tenth day of life, making daily estimations, and our results practically agree with those of Dr. Kato. We found that the cord blood of each of these infants showed a practically normal prothrombin time. This has been noted also by Nygaard and others. There was then rapid increase in the prothrombin time during the first twenty-four hours of life. The greatest increase was reached in about twenty-four to thirty-six hours. From that time there was rapid diminution in prothrombin time until the fifth or the sixth day, as Dr. Kato showed, and from then to the tenth day the level remained slightly above the adult level but apparently was the normal one for the infant.

With regard to the presence or absence of hemorrhages, there seems to be great variation in the prothrombin time at which hemorrhage occurs, for in a few cases in which the prothrombin time varied between one hundred and fifty and two hundred and fifty seconds there was no evidence of hemorrhage.

With regard to the use of vitamin K, our experience in a small number of cases has shown that after use of vitamin K the prothrombin time is quickly reduced, not to the normal level but to about twice the normal level. After that drop we have found it rather difficult to bring the prothrombin time down to the normal level by this means. However, it reaches the normal level naturally after about six to ten days.

DR. KATO, Chicago: In regard to Dr. McCune's question of using vitamin K prophylactically, I am not able to say much other than that the matter is being widely investigated, especially by obstetricians.

Apparently the hemorrhagic tendency in the newborn may be controlled by the prophylactic use of vitamin K during labor or shortly before the onset of labor. We have had several occasions to observe the effect of the administration of vitamin K at the beginning of labor, and the small collection of data thus obtained has convinced us that the administration of vitamin K to prospective mothers definitely tends to shorten the prothrombin time of their offspring. Although it is simply a conjecture, I presume that in obstetric practice vitamin K will be increasingly used.

If a newborn infant displays a tendency to bleed, the prothrombin time ought to be determined, so that vitamin K may be administered without delay. But even if no hemorrhagic tendency is present, an examination of prothrombin time made during the first day—well, I will say at the end of the first twenty-four hours—which shows prolongation indicates the use of vitamin K irrespective of the presence or absence of gross hemorrhage.

In answer to Dr. Ross's comment I wish to state that in our initial report on the prothrombin time in the newborn we failed to make it clear that we were unable to determine the prothrombin time at hourly intervals. Therefore, when we spoke of the prothrombin time on the first day of life we simply meant the aggregate of prothrombin tests performed on babies during the first twenty-four hours after birth. Not being in residence at the hospital, we just went to the

hospital at certain times each day and performed the tests for all the babies then available. Future studies, of course, ought to include hourly determinations of prothrombin time during this period. I am sure that at the end of twenty-four hours either a material increase or a definite decrease in prothrombin time will be noted, corresponding to a considerable degree of individual variation.

I think Dr. Ross mentioned that hemorrhagic symptoms may or may not occur in all babies with prolonged prothrombin time. But if a hemorrhage is not clinically manifested, e. g., an intracranial or an intraspinal hemorrhage, it is sometimes difficult to say whether or not one is taking place. I believe that some years ago a report was published on findings in the spinal fluid of 100 consecutive newborn infants in a New York hospital, in which it was stated that from 20 to 25 per cent of these babies showed evidence of hemorrhage in the spinal canal. This is an interesting and significant observation. I think a very slight trauma at the time of birth, especially if it occurs internally, is frequently missed. The determination of the prothrombin time is the only way in which a state of hypoprothrombinemia or vitamin K deficiency may be detected.

# Book Reviews

**A Manual for Diabetic Patients.** By W. D. Sansum, M.D.; Alfred E. Koehler, M.D., and Ruth Bowden, B.S. Price, $3.25. Pp. 227, with 9 illustrations. New York: The Macmillan Company, 1939.

A discussion of the physiology of nutrition and the pathology of diabetes adequate to give the patient a practical understanding of his problem is presented. Theoretic and controversial material is omitted. The advantage of a fairly liberal amount of carbohydrate, which has been made possible with insulin, is stressed, as is also the importance of protein, minerals and vitamins. The technics of examination of the urine and administration of insulin are given in detail. The warning signs of developing acidosis and what one should do for such a condition are emphasized. No mention of the use of free diet for children is made, the authors evidently not favoring it.

The second part of the book gives food values, substitution tables and menus. The patient of average intelligence should find a considerable amount of material to interest him and to give him practical help in managing his problem.

**Puericultura.** By Giovanni de Toni. Price, none given. Pp. 540, with 106 illustrations. Torino: Edizioni Minerva Medica S. A., 1939.

Giovanni de Toni has edited a textbook on puericulture (preventive individual and social pediatrics). The different chapters in the book are written by twelve collaborators. Puericulture has recently become a required subject in all high schools and universities by authority of the Italian government. This text is obviously designed for these required courses and embodies the Fascist philosophy of obtaining a bigger and healthier Italian race.

Puericulture deals with the study of eugenics, the prenatal and postnatal care of children, growth and development, physical education, child psychology, nutrition, prophylaxis against infectious diseases—both acute and chronic—and the social and medical facilities available for mothers and children in Italy. The information as given is simply expressed, and many references to the literature are included.

**Pflanzliche Rohkostdiät.** By Dr. Ulrich Grünninger and Hanna Gettler. Price, paper, 3.60 marks. Pp. 90, with no illustrations. Stuttgart: Ferdinand Enke, 1939.

The book gives the impression of having been written to order. The first third attempts to prove that a diet exclusively of raw vegetables and fruits is almost physiologic and is a remedy for most of the nutritional ailments of children. In this section are tables of analyses of fruits and vegetables, which if accurate may be serviceable. The main section consists of menus of various combinations of these raw foods, with an indication of the season when each is obtainable and the cost.

As a scientific contribution, the work is valueless. As an index of how Germany is forcing science to do its bidding, the work is enlightening.

**L'encefalografia nell'infanzia.** By R. Ruggeri. Price, 25 lire. Pp. 102, with 37 illustrations. Bologna: L. Cappelli, 1939.

Ruggeri is the chief of the section of children's neuropsychiatry in the Provincial Psychiatric Hospital of Milan. In this book he covers the subject of encephalography remarkably well and presents his material in a factual style. The facts are clearly stated, having been gathered from the literature and the author's

own clinical experience. In section I a technic of encephalography, its indications and contraindications and its physiologic and therapeutic effects are discussed. Section II covers the normal encephalogram, and section III, the encephalographic findings in thirty-one neurologic and psychiatric conditions. In the appendix the cerebral angiogram and its use in the localization of brain tumors is described.

**Your Baby—And How to Care for It.** By Dr. Lindsey W. Batten. Price, $1.50. Pp. 182, with no illustrations. New York: Harper & Brothers, 1940.

This book consists of instructions to the prospective mother, considerable material on breast feeding, its advisability and management, little discussion of artificial feeding and much advice on child training and management. The whole book is entertaining reading and contains much that will be of benefit to the mother. The reviewer divides all books of this class into two groups: those that can be safely recommended to the mother and those that cannot be. This book certainly belongs to the first group and should be on the list of every pediatrician and physician whom the young mother may ask to recommend a book on the care of the infant or child.

**Your Child's Food.** By Miriam E. Lowenberg. Second edition. Price, $2.50. Pp. 299, with 15 illustrations. New York: Whittlesey House (McGraw-Hill Book Company), 1939.

This book consists mostly of menus adequate and satisfactory to the need of the young child in either the family or the nursery school. Recipes are given for six and for thirty servings. In the early part of the book the author discusses the formation of food habits and how best to make the shifts in feeding which occur in the first two years. Constant reprimanding of children at meal time is deplored, and it is advised that the child's personality should be respected at all times.

**The Medical Career and Other Papers.** By Harvey Cushing. Price, $2.50. Pp. 302, with no illustrations. Boston: Little, Brown and Company, 1940.

This is a series of essays and short biographies from the pen of the distinguished surgeon, Harvey Cushing, whose literary fame will always be connected with "The Life of Sir William Osler." The articles, most of which are rather short, make excellent reading and are characterized by his pleasing style and independent thinking.

# Directory of Pediatric Societies*

## INTERNATIONAL

### International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

### International Congress of Pediatrics

American Committee:

Chairman: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
General Secretary: Dr. Kenneth D. Blackfan, 300 Longwood Ave., Boston.
Assistant Secretary-Treasurer: Dr. Charles F. McKhann, 300 Longwood Ave., Boston.

Canadian Committee:

Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. H. P. Wright, 1509 Sherbrooke St. W., Montreal.
Place: Boston, Mass. Time: Postponed indefinitely.

### International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

## FOREIGN

### Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

### British Paediatric Association

President: Prof. Charles McNeil, 44 Heriot Row, Edinburgh, Scotland.
Secretary: Dr. Arthur G. Maitland Jones, 31A Weymouth St., London, W. 1.

### Danish Pediatric Society

President: Dr. E. Lenstrup, Copenhagen.
Secretary: Dr. E. Gjørup, Dronning Louises Børnehospital, Copenhagen.

### Paediatrický Spolok na Slovensku

President: Dr. A. J. C. Chura, Lazaretská 11, Bratislava.
Secretary: Dr. P. Rados, Lazaretská 6, Bratislava.
Place: Pediatric Clinic, University Bratislava. Time: Six times a year.

### Royal Society of Medicine, Section for the Study of Disease in Children

President: Dr. E. A. Cockayne, 98 Harley St., London, W. 1, England.
Secretary: Dr. R. Lightwood, 86 Brook St., London, W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p. m.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

PALESTINE JEWISH MEDICAL ASSOCIATION, SECTION OF PHYSICIANS OF CHILDREN'S DISEASES

President: Prof. S. Rosenbaum, 26 Bialikstr., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

SOCIEDAD CUBANA DE PEDIATRÍA

President: Dr. Clemente Inclan Costa, Manrique 48, Habana.
Secretary: Dr. Serafin Falcon Lopez, Calle B No. 356, Vedado, Habana.
Place: Cátedra de Clinica Infantil, Hospital Mercedes, Habana. Time: Last Wednesday of every month.

SOCIEDAD MEXICANA DE PEDIATRIA

President: Dr. Jorge Muñoz Turnbull, Av. Alvaro Obregón 186, Mexico, D. F.
Secretary: Dr. Fernando López Clares, Medellín 191, Mexico, D. F.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Dr. B. Weill-Hallé, 49 Avenue Raymond Poincaré, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue du Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Malades, 49 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

## NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON PEDIATRICS

Chairman: Dr. Julius H. Hess, 104 S. Michigan Ave., Chicago.
Secretary: Dr. Hugh L. Dwyer, 315 Alameda Rd., Kansas City, Mo.
Place: Cleveland. Time: June 2-6, 1941.

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. J. B. Bilderback, 1020 S. W. Taylor St., Portland, Ore.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Place: Hotel Peabody, Memphis, Tenn. Time: Nov. 18-20, 1940.
Region I. Place: New Haven, Conn. Time: March 27-29, 1941.
Region II. Place: Richmond, Va.
Region III. Place: Palmer House, Chicago. Time: May 15-17, 1941.
Region IV. Place: San Francisco.

NORTHERN CALIFORNIA AFFILIATES

President: Dr. Crawford Bost, 490 Post St., San Francisco.
Secretary: Dr. William A. Reilly, 384 Post St., San Francisco.
Time: Second Thursday of September, November, January, March and May.

AMERICAN HOSPITAL ASSOCIATION, CHILDREN'S HOSPITAL SECTION

Chairman: Dr. D. L. Richardson, 593 Eddy St., Providence, R. I.
Secretary: Dr. Joelle C. Hiebert, 299 Main St., Lewiston, Maine.

AMERICAN PEDIATRIC SOCIETY

President: Dr. Thomas B. Cooley, 1728 Seminole Ave., Detroit.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid Ave., St. Louis.
Place: Hot Springs, Va. Time: May 22-24, 1941.

CANADIAN SOCIETY FOR THE STUDY OF DISEASES OF CHILDREN

President: Dr. L. M. Lindsay, 815 Medical Arts Bldg., Montreal.
Secretary-Treasurer: Dr. Elizabeth Chant Robertson, Hospital for Sick Children, Toronto.

### Society for Pediatric Research

President: Dr. A. Ashley Weech, 3975 Broadway, New York.
Secretary: Dr. Mitchell I. Rubin, 1740 Bainbridge St., Philadelphia.

## SECTIONAL

### Intermountain Pediatric Society

President: Dr. Eugene Smith, 385–24th St., Ogden, Utah.
Secretary-Treasurer: Dr. W. C. Cheney, 837 Boston Bldg., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

### New England Pediatric Society

President: Dr. R. Cannon Eley, 319 Longwood Ave., Boston.
Secretary-Treasurer: Dr. James Marvin Baty, 319 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Four meetings a year, occurring from September to May.

### North Pacific Pediatric Society

President: Dr. S. G. Henricke, 4215 N. E. Hancock St., Portland, Ore.
Secretary: Dr. J. S. Backstrand, 333 Wyatt Court, Salem, Ore.

### Rocky Mountain Pediatric Society

President: Dr. Donn Barber, 802½–8th Ave., Greeley, Colo.
Secretary: Dr. Kenneth Schmidt, Republic Bldg., Denver.
Place: Children's Hospital, Denver. Time: First Saturday of each month from September to May, inclusive, 7:30 p. m.

### Southern Medical Association, Section of Pediatrics

Chairman: Dr. Harvey F. Garrison, 319 E. Capitol St., Jackson, Miss.
Secretary: Dr. Warren W. Quillian, 227 Aragon Ave., Coral Gables, Fla.
Place: Louisville Ky. Time: Nov. 12-15, 1940.

## STATE

### Alabama Pediatric Society

President: Dr. Stewart H. Welch, 1117 S. 20th St., Birmingham.
Secretary-Treasurer: Dr. William R. Britton, 4 Catoma St., Montgomery.
Place: Birmingham. Time: Sept. 18, 1940.

### Arkansas State Pediatric Association

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

### California State Medical Society, Section on Pediatrics

Chairman: Dr. William Belford, 233 A St., San Diego.
Secretary: Dr. Louis M. Earle, 6381 Hollywood, Hollywood, Calif.
Place: Del Monte. Time: May 1941.

### Florida State Pediatric Society

President: Dr. Warren W. Quillian, 227 Aragon Ave., Coral Gables.
Secretary: Dr. George N. Leonard, 605 Lincoln Rd., Miami Beach.
Place: Concurrent with state association meeting at time of convention.

### Georgia Pediatric Society

President: Dr. R. C. McGahee, 1345 Greene St., Augusta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.

### Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. Oliver L. Stringfield, 1416 Bedford St., Stamford.
Secretary: Dr. Joseph L. Hetzel, 103 N. Main St., Waterbury.
Time: Three meetings a year.

### Illinois State Medical Society, Section on Pediatrics

Chairman: Dr. Orville Barbour, 331 Fulton St., Peoria.
Secretary: Dr. Craig Butler, 715 Lake St., Oak Park.
Place: Chicago. Time: May 1941.

### Indiana State Pediatric Society

President: Dr. K. T. Knode, 1105 E. Jefferson Blvd., South Bend.
Secretary-Treasurer: Dr. Mathew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

### Iowa Pediatric Society

President: Dr. Morgan J. Foster, 837 Higley Bldg., Cedar Rapids.
Secretary-Treasurer: Dr. Arnold M. Smythe, 406–6th Ave., Des Moines.

### Louisiana State Pediatric Society

President: Dr. H. Aubrey White, Alexandria.
Secretary-Treasurer: Dr. W. C. Rivenbark, 3503 Prytania St., New Orleans.
Place: Shreveport. Time: April 1941.

### Medical Society of State of New York, Section on Pediatrics

Chairman: Dr. Norman L. Hawkins, 11 Public Sq., Watertown, N. Y.
Secretary: Dr. William J. Orr, 135 Linwood Ave., Buffalo.

### Medical Society of the State of Pennsylvania, Pediatric Section

Chairman: Dr. Ralph M. Tyson, 255 S. 17th St., Philadelphia.
Secretary: Dr. John D. Sturgeon Jr., 22 N. Gallatin Ave., Uniontown.
Place: Philadelphia, Pa. Time: Sept. 30-Oct. 3, 1940.

### Michigan State Medical Society, Pediatric Section

President: Dr. Ward L. Chadwick, 524 Medical Arts Bldg., Grand Rapids.
Chairman: Dr. Harry Towsley, University of Michigan Hospital, Ann Arbor.
Place: Detroit. Time: Sept. 25-27, 1940.

### Mississippi State Pediatric Society

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.
Place: Biloxi. Time: May 12, 1941.

### Nebraska Pediatric Society

President: Dr. Herman M. Jahr, 1120 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. Elmer W. Bantin, 440 Aquila Court Bldg., Omaha.
Place: As announced by committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

### New Hampshire Pediatric Society

President: Dr. Colin C. Stewart, Hitchcock Clinic, Hanover.
Secretary-Treasurer: Dr. Ursula G. Sanders, 46 Pleasant St., Concord.
Time: Twice yearly.

### North Carolina Pediatric Society

President: Dr. Marion Y. Keith, 369 N. Elm St., Greensboro.
Secretary: Dr. G. W. Kutscher Jr., 176 Woodfin St., Asheville.

### Oklahoma State Pediatric Society

President: Dr. Ben H. Nicholson, 301 N.W. 12th St., Oklahoma City.
Secretary: Dr. Luvern Hays, 108 W. 6th St., Tulsa.
Place: Oklahoma Club. Time: 6:30 p. m., fourth Friday of each alternate month from September to May, inclusive.

### South Carolina Pediatric Society

President: Dr. R. B. Josey, 1517 Hampton Ave., Columbia.
Secretary-Treasurer: Dr. Wilson Ball, South Carolina State Health Dept., Columbia.

### Tennessee State Pediatric Society

President: Dr. Kinsey M. Buck, 1193 Madison Ave., Memphis.
Secretary: Dr. Gilbert Eblen, 607 Medical Arts Bldg., Knoxville.

### Texas Pediatric Society

President: Dr. C. P. Jasperson, 509 Nixon Bldg., Corpus Christi.
Secretary-Treasurer: Dr. F. H. Lancaster, 4409 Fannin St., Houston.
Place: Galveston. Time: Oct. 5, 1940.

### Virginia Pediatric Society

President: Dr. S. A. Anderson Jr., 2326 W. Grace St., Richmond.
Secretary: Dr. John M. Bishop, 511 Medical Arts Bldg., Roanoke.
Place: White Sulphur Springs, W. Va. Time: July 24, 1940.

### West Virginia State Medical Society, Section on Pediatrics

President: Dr. Raymond Sloan, 1139–4th Ave., Huntington.
Secretary: Dr. Thomas G. Folsom, 1139–4th Ave., Huntington.
Place: White Sulphur Springs. Time: July 29-31, 1940.

## LOCAL

### Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. J. D. Nourse, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. I. B. Silber, 10465 Carnegie Ave., Cleveland.
Place: Cleveland Medical Library Bldg. Time: October, December, February and April.

### Academy of Medicine, Toronto, Section of Pediatrics

President: Dr. T. B. Verner, 170 St. George St., Toronto, Canada.
Secretary: Dr. D. V. Hutton, 170 St. George St., Toronto, Canada.

### Bronx Pediatric Society

President: Dr. Harry S. Altman, 940 Grand Concourse, New York.
Secretary: Dr. David Zahn, 2474 Valentine Ave., New York.
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Every second Wednesday of each month, except June, July, August and September.

### Brooklyn Academy of Pediatrics

President: Dr. Archibald Smith, Garden City, N. Y.
Secretary: Dr. Walter Coles, 604–2d St., Brooklyn.
Place: Kings County Medical Society Bldg. Time: Fourth Wednesday of each month, except May, June, July, August and September.

### Central New York Pediatric Club

President: Dr. Frank van der Bogert, 111 Union St., Schenectady.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Place: Various cities in New York. Time: Third Tuesday of April and September.

### Chicago Pediatric Society

President: Dr. Philip Rosenblum, 2376 E. 71st St., Chicago.
Secretary: Dr. Bengt Hamilton, 826 E. 61st St., Chicago.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May, inclusive.

### Dallas Pediatric Society

President: Dr. Edgar Loomis, 351 W. Jefferson Ave., Dallas, Texas.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmont Ave., Dallas, Texas.
Place: Bradford Baby Hospital. Time: 1 p. m., second and fourth Saturdays of each month.

### Detroit Pediatric Society

President: Dr. Robert J. Mason, 460 Birmingham Rd., Birmingham, Mich.
Secretary: Dr. J. Hugh Lewis, 2966 Biddle Ave., Wyandotte, Mich.
Place: Wayne County Medical Society. Time: 8:30 p. m., first Wednesday of each month from October to June, inclusive.

### Fulton County Medical Society, Pediatric Section (Atlanta, Ga.)

Chairman: Dr. Stephen C. Redd, 157 Forrest Ave. N. E., Atlanta.
Secretary: Dr. C. Dixon Fowler, Medical Arts Bldg., Atlanta.
Place: Academy of Medicine, 38 Prescott St. N. E. Time: Second Thursday of each month from October to April, 8 p. m.

### Houston Pediatric Society

President: Dr. Thomas J. Donovan, 3820 Fannin St., Houston, Texas.
Secretary: Dr. Raymond Cohen, 2300 Caroline St., Houston, Texas.
Place: Houston Club. Time: Third Monday of each month.

### Kansas City (Missouri) Pediatric Society

President: Dr. John Aull, 1103 Grand Ave., Kansas City.
Secretary: Dr. George Herrman, 1107 Bryant Bldg., Kansas City.
Place: Kansas City General Hospital. Time: On call.

### Los Angeles County Medical Association, Pediatric Section

President: Dr. Alonzo Cass, 1908 Wilshire Blvd., Los Angeles.
Secretary-Treasurer: Dr. Gladys Patric Shahovitch, 3936 Roderick Rd., Los Angeles.
Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

### Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Sydney Nussbaum, 247 Ocean View Ave., Brooklyn.
Secretary: Dr. Harry Bikoff, 850 St. Marks Ave., Brooklyn.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., second Monday of each month, October to March, inclusive.

### Medical Society of the County of Queens, Inc., Section on Pediatrics

Chairman: Dr. A. A. Trivilino, 88-07–150th St., Jamaica, N. Y.
Secretary-Treasurer: Dr. Edith A. Mittell, 144–38th Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

### Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. Harry A. Ong, 1801 I St. N. W., Washington, D. C.
Secretary-Treasurer: Dr. William F. Burdick, 5402 Connecticut Ave. N. W., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N. W. Time: 8 p. m., fourth Thursday of every month.

### Memphis Pediatric Society

President: Dr. E. C. Mitchell, 1073 Madison Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. Harry Jacobson, 1193 Madison Ave., Memphis, Tenn.
Place: John Gaston Hospital. Time: Quarterly.

### Milwaukee Pediatric Society

President: Dr. S. F. Morgan, 2577 N. Downer Ave., Milwaukee.
Secretary-Treasurer: Dr. F. R. Janney, 1411 Wauwatosa Ave., Wauwatosa, Wis.
Place: Children's Hospital. Time: Second Wednesday of each alternate month, beginning with February.

### New York Academy of Medicine, Section of Pediatrics

Chairman: Dr. Leslie O. Ashton, 850 Park Ave., New York.
Secretary: Dr. Alfred Langmann, 108 E. 68th St., New York.
Place: New York Academy of Medicine, 2 E. 103 St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

### Northwestern Pediatric Society

President: Dr. Roland E. Nutting, 205 W. 2d St., Duluth, Minn.
Secretary-Treasurer: Dr. John M. Adams, 1009 Nicollet Ave., Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

### Oklahoma City Pediatric Society

President: Dr. J. Byron Snow, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. G. R. Felts, 1200 N. Walker St., Oklahoma City.
Place: Oklahoma Club. Time: Third Friday of each alternate month.

### Philadelphia Pediatric Society

President: Dr. Pascal F. Lucchesi, 4000 N. Front St., Philadelphia.
Secretary: Dr. Aims C. McGuinness, Children's Hospital, 1740 Bainbridge St., Philadelphia.
Place: College of Physicians, 19 S. 22d St. Time: Second Tuesday of each month from October to April, inclusive.

### Pittsburgh Pediatric Society

President: Dr. E. L. Piper, 3200–5th Ave., Pittsburgh.
Secretary-Treasurer: Dr. Carl Ruder, 646 Washington Rd., Mount Lebanon, Pittsburgh.
Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate month from October to June, inclusive.

### Richmond Pediatric Society

President: Dr. Charles L. Outland, 312 N. 9th St., Richmond, Va.
Secretary-Treasurer: Dr. T. Stanley Meade, 913 Floyd Ave., Richmond, Va.
Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: 8 p. m., third Thursday of each month, except June, July and August.

### Rochester Pediatric Society

President: Dr. David Wolin, 16 N. Goodman St., Rochester, N. Y.
Secretary: Dr. W. L. Bradford, 16 N. Goodman St., Rochester, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee. Time: Third Friday of each month from October to May.

### St. Louis Pediatric Society

President: Dr. Max Deutch, 634 N. Grand Blvd., St. Louis.
Secretary-Treasurer: Dr. Peter G. Danis, 634 N. Grand Blvd., St. Louis.
Place: St. Louis Medical Society Bldg. Time: First Friday of each month from October to June.

### Seattle Pediatric Society

President: Dr. Jay I. Durand, 1305–4th Ave., Seattle.
Secretary: Dr. Frederick B. Joy, 1215–4th Ave., Seattle.
Place: College Club. Time: Third Friday of each month, 6:30 p. m.

### Southwestern Pediatric Society

President: Dr. Norman Nixon, 1136 W. 6th St., Los Angeles.
Secretary: Dr. Donald C. Shelby, 3780 Wilshire Blvd., Los Angeles.
Place: Jonathan Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

### University of Michigan Pediatric and Infectious Disease Society

President: Dr. Mark Osterlin, Central Michigan Children's Clinic, Traverse City, Mich.
Secretary: Dr. D. Murray Cowie, University of Michigan, Ann Arbor, Mich.
Time: Nov. 15-16, 1940.

### Westchester County Medical Society, Pediatric Section (New York)

President: Dr. M. Bernard Brahdy, 531 E. Lincoln Ave., Mount Vernon.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Ave., Rye.
Place: Grasslands Hospital, Valhalla, N. Y. Time: Third Thursday in October, December, February and April.